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(54) **VECTOR PARTICLES FOR TARGETING CD34+ CELLS**

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USPC **435/320.1; 530/350**

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**
The present invention relates to a vector particle for transferring biological material into cells, wherein said vector particle comprises at least: —a first protein which comprises the transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein, and —a second protein which comprises a ligand of the c-Kit receptor.

17 Claims, 4 Drawing Sheets

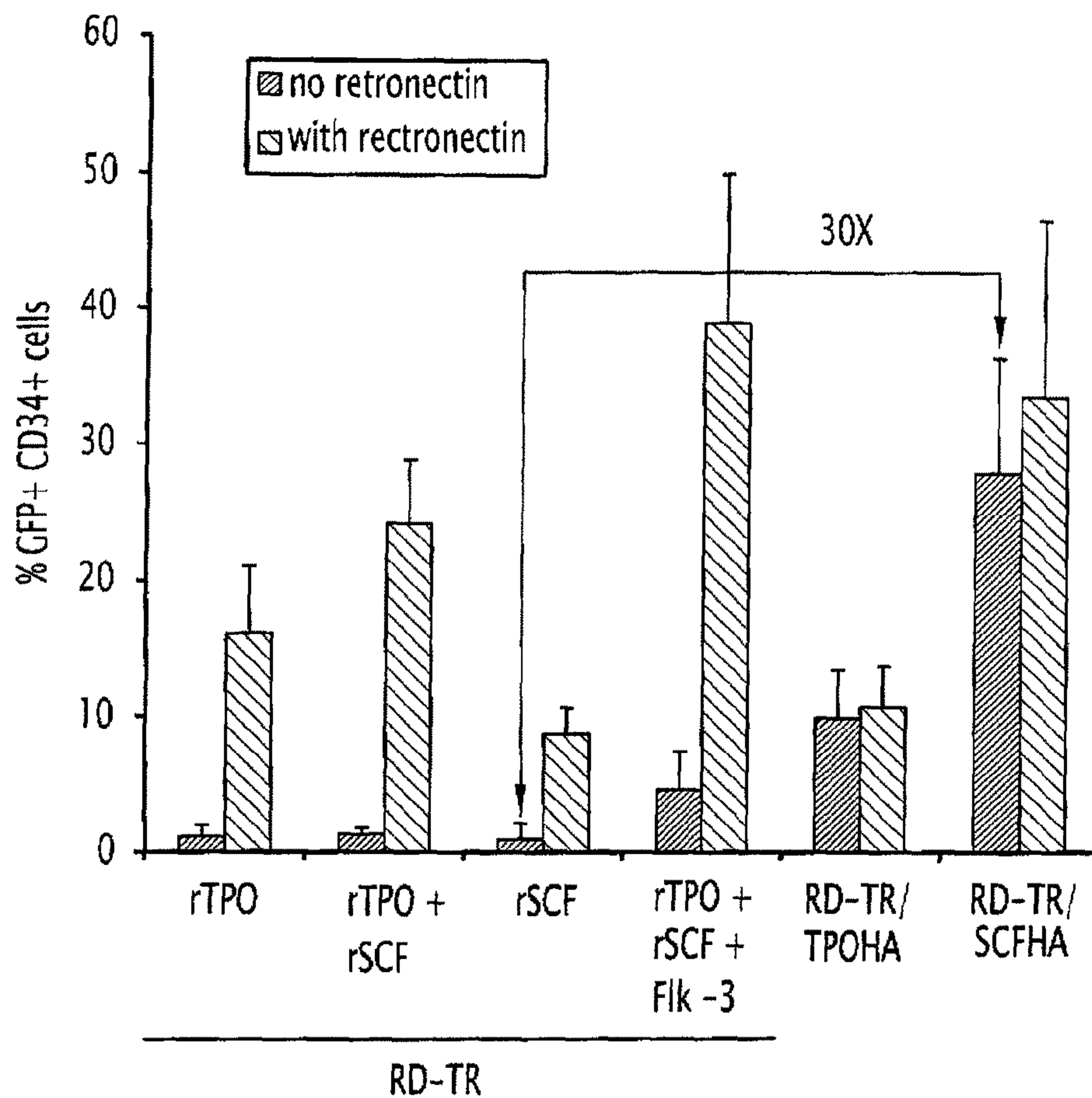


FIG. 1

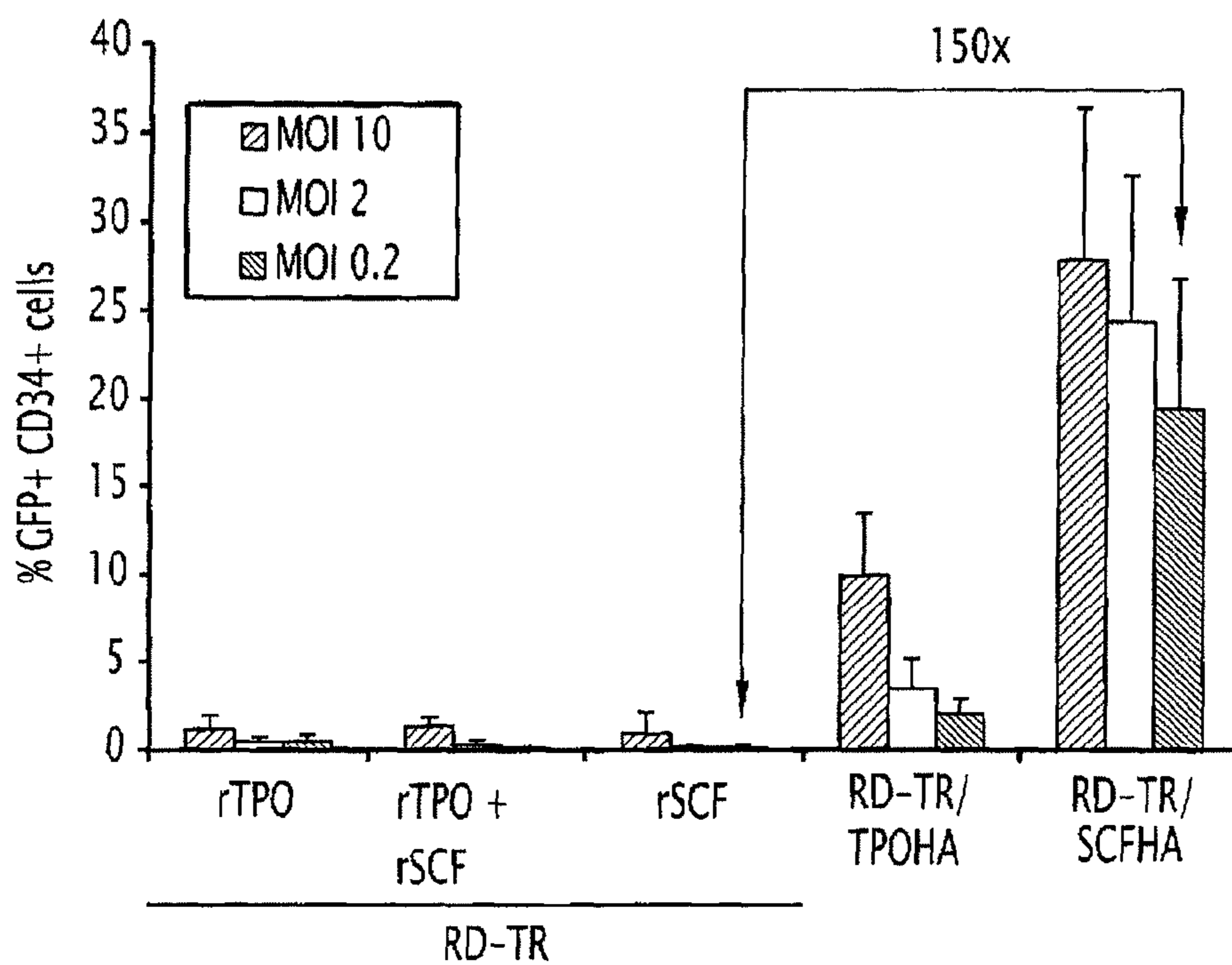


FIG. 2

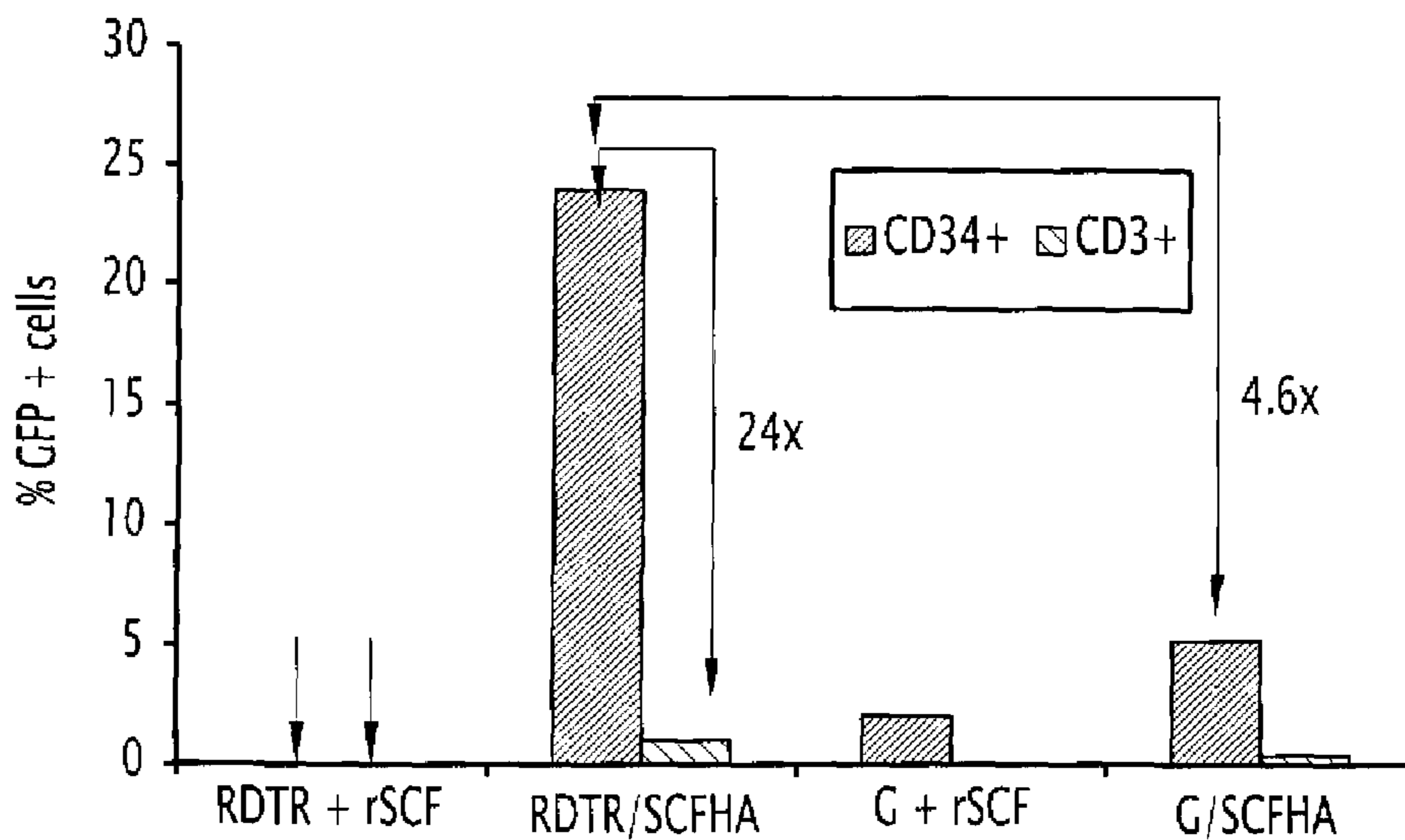


FIG. 3

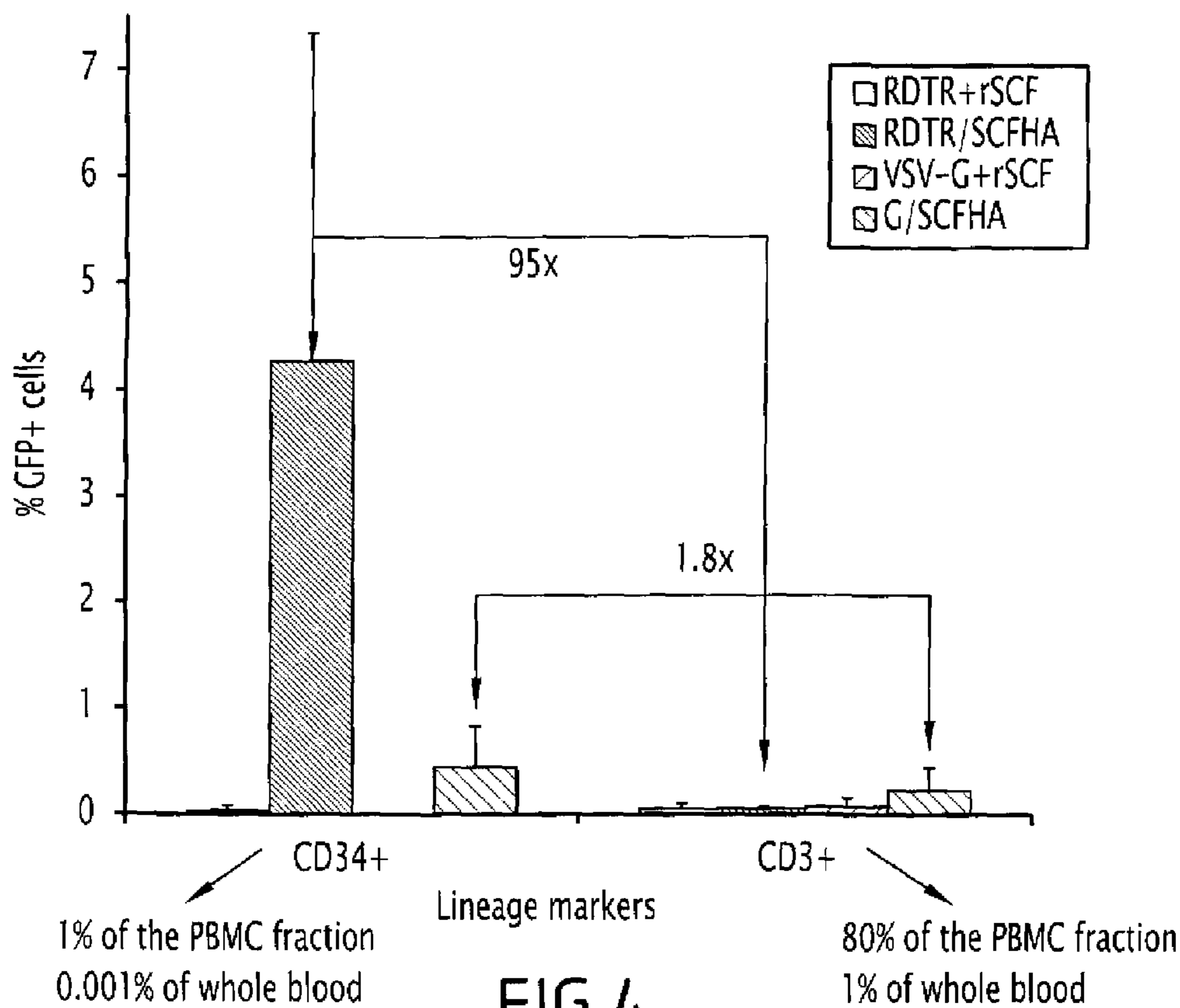


FIG. 4

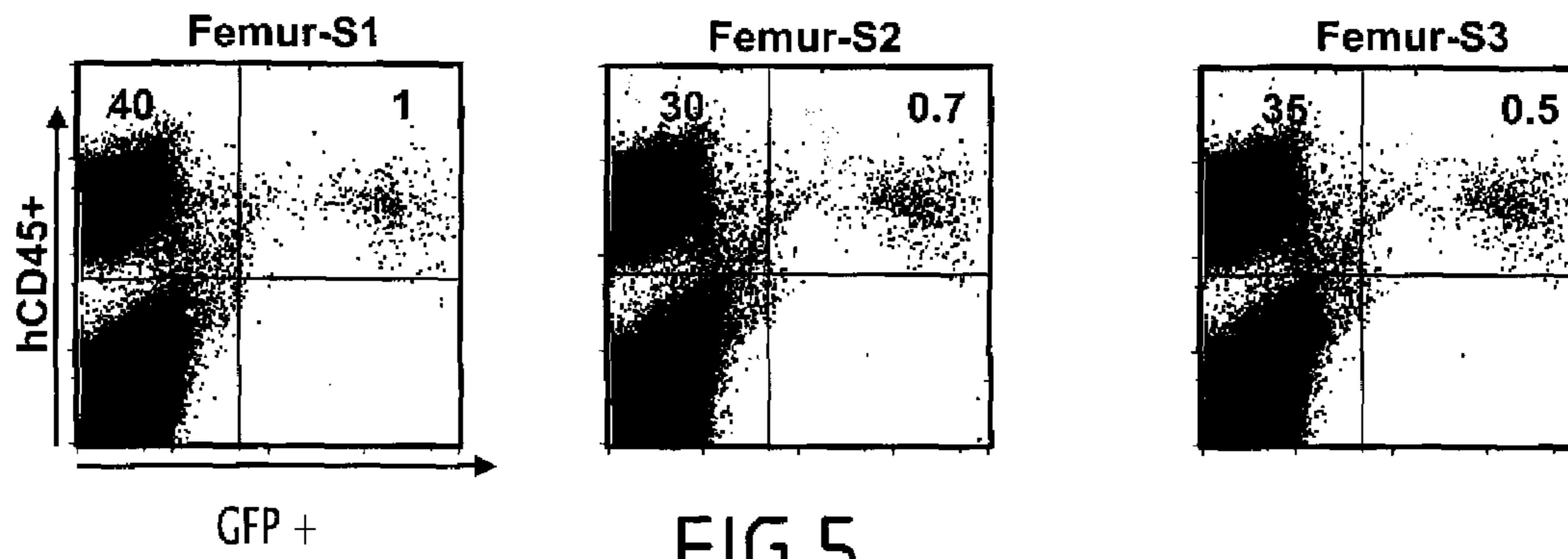


FIG.5

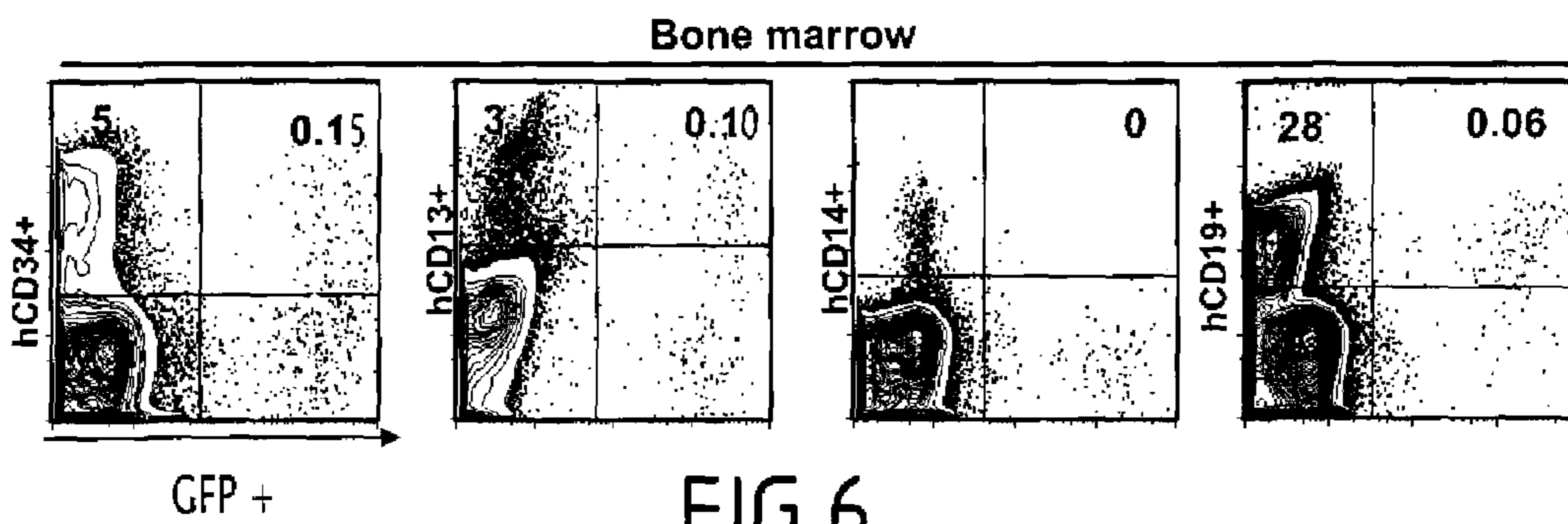


FIG.6

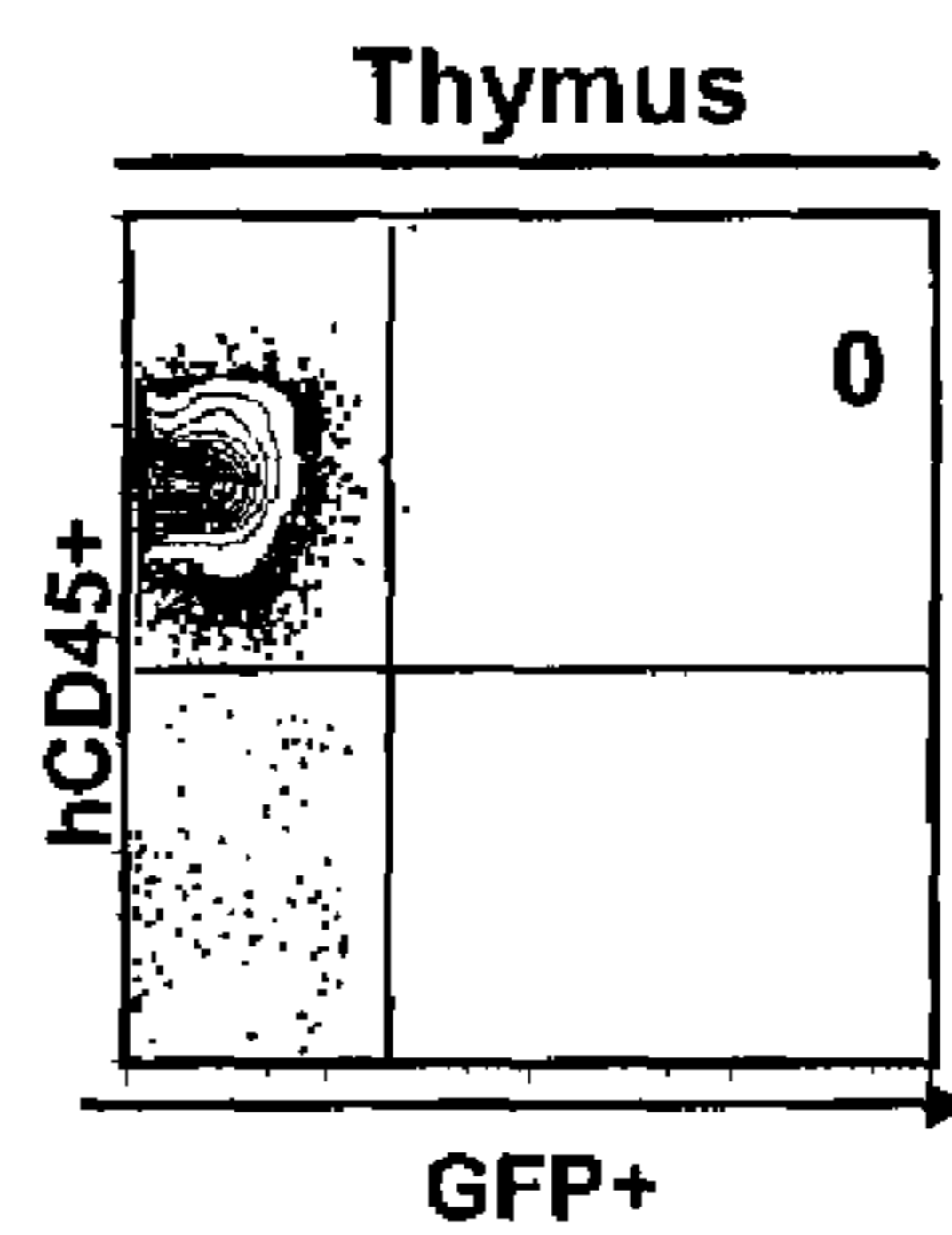


FIG.7

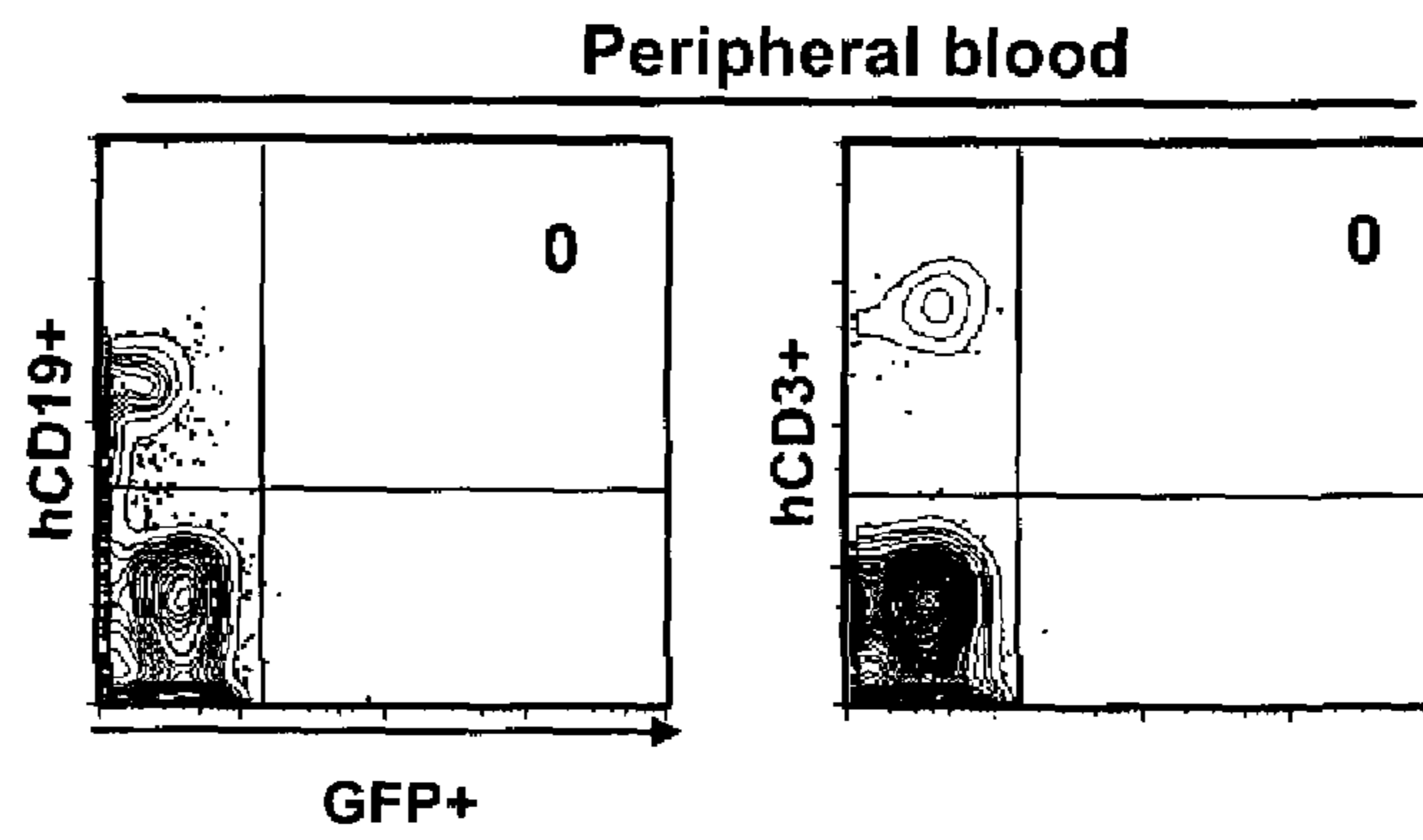


FIG.8

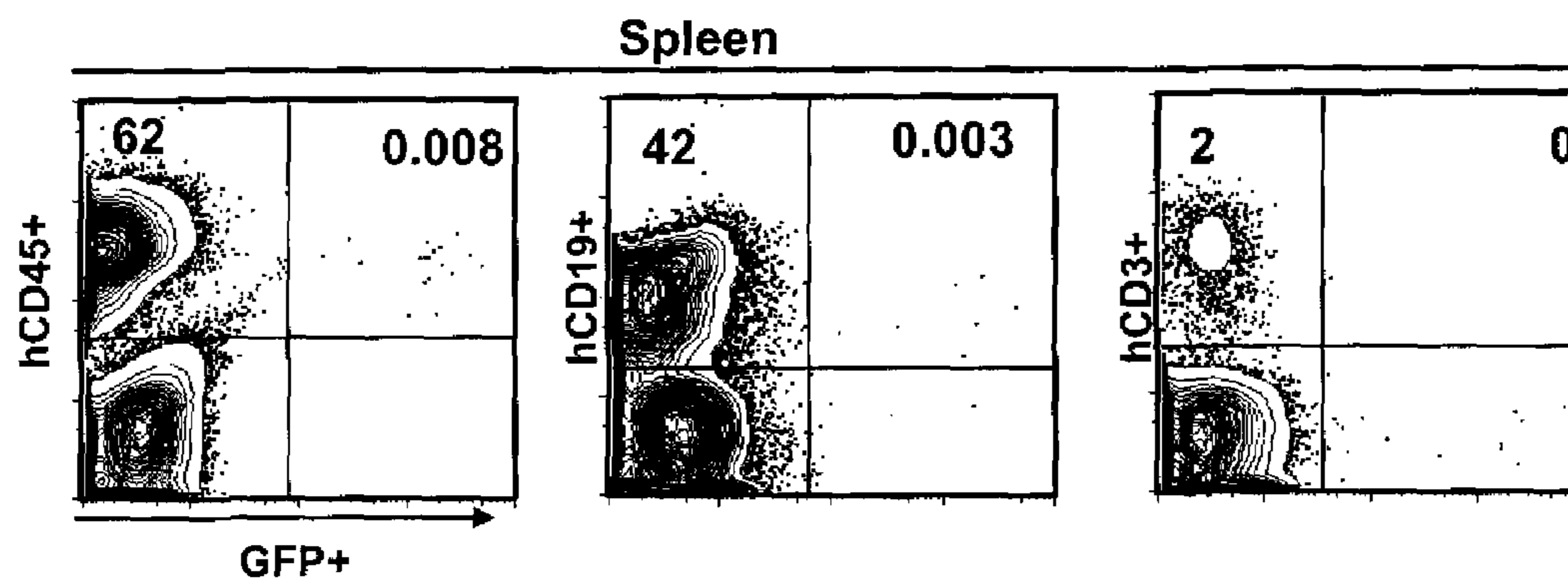


FIG.9

VECTOR PARTICLES FOR TARGETING CD34⁺ CELLS

The present invention relates to vector particles intended for the specific delivery of biological material to cells.

For the correction by gene therapy of many inherited or acquired defects of the hematopoietic system, the therapeutic gene must be delivered to cells able both to self-renew and to differentiate into all hematopoietic lineages. As such, these gene therapies must be targeted to the “right” cells, i.e. hematopoietic stem cells (HSCs), without modifying their properties. The population of choice for targeting HSCs is constituted of CD34⁺ progenitor cells, which are particularly enriched in these stem cells. However, CD34⁺ cells only represent 0.001% of the total blood cells for instance. Accordingly, to avoid the cumbersome steps of cell extraction, culture in the presence of multiple growth factors or transduction adjuvants, and infusion into the patient, the vector particles have to display a very high specificity towards CD34⁺ cells, in order to allow transduction of CD34⁺ cells in non-purified bodily samples, such as blood samples, or to ensure an efficient in vivo transduction of CD34⁺ cells despite dilution of the vector particles.

Thus, Sandrin et al. (2002) *Blood* 100:823-832 have devised Simian Immunodeficiency Virus (SIV)-derived vector particles which display a chimeric envelope glycoprotein, RDTR, constituted of the fusion of the transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein and the cytoplasmic domain of the Murine Leukemia Virus-A envelope glycoprotein. Such vector particles are also disclosed in WO 03/91442. When using a transduction adjuvant, such as RetroNectin®, the transduction rate obtained using vector particles displaying the chimeric RDTR protein is of approximately the same rate as that observed with SIV-derived vector particles displaying the Vesicular Stomatitis Virus (VSV) G envelope glycoprotein. However, in the absence of transduction adjuvant, the RDTR vector particles exhibit a much lower transduction of isolated CD34⁺ cells than vectors displaying the VSV-G glycoprotein. Besides, no particular selectivity towards CD34⁺ cells has been shown to be associated to RDTR, since vector particles displaying this chimeric protein transduce CD34⁺ cells and peripheral blood lymphocytes with approximately the same efficiency.

In another attempt at targeting CD34⁺ cells, Verhoeyen et al. (2005) *Blood* 106:3386-3395 have devised HIV-1-derived vector particles which display the VSV-G envelope glycoprotein and so-called early acting cytokines, namely Thrombopoietin (TPO) and Stem Cell Factor (SCF). The authors have thus shown that these vector particles provided for efficient transduction of isolated CD34⁺ cells. However, no targeting specificity of these vector particles could be evidenced.

Accordingly, it is an object of the present invention to provide vector particles which are more efficient than those of the prior art at specifically targeting CD34⁺ cells.

SUMMARY OF THE INVENTION

The present invention arises from the discovery, by the inventors, that the co-display of RDTR and SCF on HIV-derived vector particles had unexpected synergic effects on the efficiency and the specificity of transduction of CD34⁺ cells. Advantageously, such vector particles are not dependent on RetroNectin® to achieve transduction, can effect efficient transduction at low dosage, and are capable to transduce CD34⁺ cells in fresh whole blood.

Thus, the present invention relates to a vector particle for transferring biological material into cells, wherein said vector particle comprises at least:

- a first protein which comprises the transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein, and
- a second protein which comprises a ligand of the c-Kit receptor.

The present invention also relates to the use of (i) a first nucleic acid comprising a sequence encoding a first protein as defined above and of (ii) a second nucleic acid comprising a sequence encoding a second protein as defined above, for preparing a vector particle for transferring biological material into cells and in particular for preparing a vector particle as defined above.

The present invention also relates to a method for preparing a vector particle for transferring biological material into cells and in particular for preparing a vector particle as defined above, wherein (i) a first nucleic acid comprising a sequence encoding a first protein as defined above and (ii) a second nucleic acid comprising a sequence encoding a second protein as defined above, are transferred in a producer cell, and the vector particle is recovered from said producer cell.

The present invention also relates to a medicament comprising a vector particle as defined above as active ingredient.

The present invention also relates to a method for treating an individual in need of gene therapy, wherein a therapeutically effective amount of a vector particle as defined above is administered to the individual.

The present invention further relates to the use of a vector particle as defined above, for transferring the biological material into cells ex vivo.

The present invention also relates to a method for preparing cells intended for treating an individual, wherein cells to be administered to the individual are contacted with a vector particle as defined above.

The present invention also relates to a method for treating an individual in need of gene therapy, wherein in a first step cells to be administered to the individual are contacted with a vector particle as defined above and in a second step said cells are administered to the individual.

The present invention also relates to a protein represented by SEQ ID NO: 4.

The present invention also relates to a nucleic acid encoding a protein of sequence SEQ ID NO: 4.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 represents the percentage of CD34⁺ cells (vertical axis) transduced by GFP-encoding HIV-derived vector particles displaying RDTR only, in the presence of recombinant TPO (10 ng/ml) or recombinant SCF (50 ng/ml), or vector particles displaying RDTR and TPOHA, or RDTR and SCFHA, in the presence (widely hatched bars) or absence (closely hatched bars) of RetroNectin®.

FIG. 2 represents the percentage of CD34⁺ cells (vertical axis) transduced by GFP-encoding HIV-derived vector particles displaying RDTR only, in the presence of recombinant TPO (10 ng/ml) or recombinant SCF (50 ng/ml), or vector particles displaying RDTR and TPOHA, or RDTR and SCFHA, at a Multiplicity Of Infection (M.O.I.) of 10 (widely hatched bars), 2 (white bars) or 0.2 (closely hatched bars) as determined on HeLa cells.

FIG. 3 represents the percentage of GFP expressing cells (vertical axis) present in a PBMC population isolated from cord blood transduced by GFP-encoding HIV-derived vector particles displaying RDTR only in the presence of recombi-

nant SCF (50 ng/ml), RDTR and SCFHA, VSV-G only in the presence of recombinant SCF (50 ng/ml), or VSV-G and SCFHA, wherein the cells are CD34⁺ cells (closely hatched bars) or CD3⁺ cells (widely hatched bars).

FIG. 4 represents the percentage (vertical axis) of GFP expressing CD34⁺ cells or CD3⁺ cells present in whole cord blood transduced by GFP-encoding HIV-derived vector particles displaying RDTR only in the presence of recombinant SCF (50 ng/ml) (first bar), RDTR and SCFHA (second bar), VSV-G only and recombinant SCF (50 ng/ml) (third bar), or VSV-G and SCFHA (fourth bar).

FIG. 5 represents the analysis by fluorescence-activated cell sorter (FACS) of the transduction (GFP⁺) of total human cells in the bone marrow. The three histograms show respectively the results obtained on three different injected mice. The cells were sorted according to hCD45 expression (hCD45⁺, vertical axis) and GFP expression (GFP⁺, horizontal axis).

FIG. 6 represents the analysis by FACS of the transduction (GFP⁺) of early progenitors (hCD34⁺), myeloid progenitors (hCD13⁺), monocytes (hCD14⁺) and pre- and pro B-cells (hCD19⁺) in the bone marrow. The first histogram shows the results obtained with cells sorted according to hCD34 expression (hCD34⁺, vertical axis) and GFP expression (GFP⁺, horizontal axis). The second histogram shows the results obtained with cells sorted according to hCD13 expression (hCD13⁺, vertical axis) and GFP expression (horizontal axis). The third histogram shows the results obtained with cells sorted according to hCD14 expression (hCD14⁺, vertical axis) and GFP expression (horizontal axis). The fourth histogram shows the results obtained with cells sorted according to hCD19 expression (hCD19⁺, vertical axis) and GFP expression (horizontal axis).

FIG. 7 represents the analysis by FACS of the transduction (GFP⁺) of human thymocytes in the thymus. The cells were sorted according to hCD45 expression (hCD45⁺, vertical axis) and GFP expression (GFP⁺, horizontal axis).

FIG. 8 represents the analysis by FACS of the transduction (GFP⁺) of B-cells (hCD19⁺) and T-cells (hCD3⁺) in the peripheral blood. The first histogram shows the results obtained with cells sorted according to hCD19 expression (hCD19⁺, vertical axis) and GFP expression (GFP⁺, horizontal axis). The second histogram shows the results obtained with cells sorted according to hCD3 expression (hCD3⁺, vertical axis) and GFP expression (horizontal axis).

FIG. 9 represents the analysis by FACS of the transduction (GFP⁺) of human splenocytes (hCD45⁺), B-cells (hCD19⁺) and T-cells (hCD3⁺) in the spleen. The first histogram shows the results obtained with cells sorted according to hCD45 expression (hCD45⁺, vertical axis) and GFP expression (GFP⁺, horizontal axis). The second histogram shows the results obtained with cells sorted according to hCD19 expression (hCD19⁺, vertical axis) and GFP expression (horizontal axis). The third histogram shows the results obtained with cells sorted according to hCD3 expression (hCD3⁺, vertical axis) and GFP expression (horizontal axis).

DETAILED DESCRIPTION OF THE INVENTION

As intended herein, “vector particle” denotes any particle liable to display the first protein and the second protein at its surface and to reversibly bind to a biological material.

It is preferred that such a vector particle is a viral vector particle, in particular a lentiviral vector particle, such as a lentiviral vector particle selected from the group consisting of Human Immunodeficiency Virus (HIV), e.g. HIV-1 or HIV-2, and Simian Immunodeficiency Virus (SW).

Lentiviral vector particles are well-known to the man skilled in the art and are notably described in Naldini et al. (2000) *Adv. Virus Res.* 55:599-609 and Negre et al. (2002) *Biochimie* 84:1161-1171. Usually, lentiviral vector particles according to the invention comprise at least the following components: (i) an envelope component, which is constituted of a phospholipidic bilayer associated to envelope proteins, wherein the envelope proteins comprise at least the above-defined first and second proteins, said envelope surrounding (ii) a core component, constituted of the association of a gag protein, said core itself surrounding (iii) genome components, usually constituted of ribonucleic acids (RNA), and (iv) an enzyme component (pol). The biological material can be present within the envelope, within the core and/or within the genome components.

Lentiviral vector particles can be readily prepared by the man skilled in the art, for example by following the general guidance provided by Sandrin et al. (2002) *Blood* 100:823-832. Briefly, the lentiviral vector particles may be generated by co-expressing the packaging elements (i.e. the core and enzyme components), the genome component and the envelope component in a so-called producer cell, e.g. 293T human embryonic kidney cells. Typically from three to four plasmids may be employed, but the number may be greater depending upon the degree to which the lentiviral components are broken up into separate units.

Generally, one plasmid encodes the core (gag) and enzymatic (pol) lentiviral components of the vector particle. The origin of the gag and pol genes gives its name to the lentiviral vector particle. For instance the expression “HIV-1-derived vector particle” usually indicates that the gag and pol genes of the vector particle are those of HIV-1. This plasmid is termed the packaging plasmid. One or several other plasmids encode the proteins which are part of the envelope. In the present case these plasmids may notably encode the first and the second protein. As will be clear to one of skill in the art, the above defined first and second nucleic acid may be either distinct or fused. Yet another plasmid encodes the genome.

As intended herein the expression “biological material” relates to one or more compounds liable to alter the structure and/or the function of a cell. Within the context of the present invention, it is preferred that the biological material is one or more nucleic acids, which in the case of lentiviral vector particles may be comprised within the genome of the vector particle. The genome typically comprises the one or more nucleic acids, preferably linked to genetic elements necessary for their expression in the target cell, such as promoters and terminators, flanked by cis-acting elements necessary for the inclusion of the genome in the core element, its reverse transcription into deoxyribonucleic acid (DNA), the import of the retrotranscribed genome into the nucleus of the target cell and the integration of the retrotranscribed genome within the genome of the target cell.

As intended herein the recipient cells for the biological material to be transferred, or target cells, relate to any cell liable to be bound by the above-defined vector particle. Where the vector particle is a lentiviral vector particle the target cell relates to any cell liable to be transduced by the vector particle. These cells usually express the c-Kit receptor which binds to the c-Kit ligand of the first protein. As such, the cells preferably targeted by the vector particle of the invention are CD34⁺ cells, in particular human CD34⁺ cells, and more particularly Hematopoietic Stem Cells (HSCs), notably human HSCs.

As intended herein “transferring” relates to the capacity of the vector particle to initially deliver the biological material to the membrane or the cytoplasm of the target cell, upon being

bound to the target cell. After delivery, the biological material can be translocated to other compartment of the cell.

The feline endogenous RD114 virus envelope glycoprotein is notably described in Cosset et al. (1995) *J. Virol.* 69:7430-7436. By way of example, the RD114 virus envelope glycoprotein corresponds to GenBank accession number X87829. Portions of RD114 corresponding to the transmembrane and extracellular domains can be readily identified by the man skilled in the art.

As intended herein, the expression "transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein" relates to transmembrane and extracellular domains of a natural feline endogenous RD114 virus envelope glycoprotein or to any mutant thereof derived therefrom by deletion, insertion or substitution of one or several amino acids, provided that said mutant presents essentially the same properties as the transmembrane and extracellular domains of the natural feline endogenous RD114 virus envelope glycoprotein from which it derives.

As intended herein, a mutant will be said to present essentially the same properties as the transmembrane and extracellular domains of a natural feline endogenous RD114 virus envelope glycoprotein from which it derives, if, when replacing the transmembrane and extracellular domains of a natural feline endogenous RD114 virus envelope glycoprotein in a reference vector particle according to the invention carrying a first protein of sequence SEQ ID NO: 2 and a second protein of sequence SEQ ID NO: 4, the mutant-carrying vector particle presents at least 30%, preferably at least 50%, more preferably at least 75%, of the transduction of CD34⁺ cells which can be observed with the reference vector particle. Preferably, the transduction conditions are those set forth in Example 2.

By way of example, the transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein are represented by SEQ ID NO: 5.

Preferably, the first protein comprises or consists in a fusion of the transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein and the cytoplasmic domain of a retroviral envelope glycoprotein. In this fusion it is preferred that the C-terminus of the transmembrane domain of RD114 is fused to the N-terminus of the cytoplasmic domain of a retroviral envelope glycoprotein.

More preferably, the first protein comprises or consists in a fusion of the transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein and the cytoplasmic domain of the Murine Leukemia Virus-A envelope glycoprotein. In this fusion it is preferred that the C-terminus of the transmembrane domain of RD114 is fused to the N-terminus of the cytoplasmic domain of MLV-A envelope glycoprotein.

The Murine Leukemia Virus-A envelope glycoprotein is notably described in Ott et al. (1990) *J. Virol.* 64:757-766. Preferably, the Murine Leukemia Virus-A envelope glycoprotein is that of strain 4070A. The portion of Murine Leukemia Virus-A envelope glycoprotein corresponding to the intracellular domain can be readily identified by the man skilled in the art. By way of example the intracellular domain of Murine Leukemia Virus-A envelope glycoprotein is represented by SEQ ID NO: 6.

Most preferably, the first protein is represented by SEQ ID NO: 2 and is in particular encoded by SEQ ID NO: 1. A preferred plasmid for expressing the first protein in a producer cell is represented by SEQ ID NO: 11.

The c-Kit receptor is well known to the man skilled in the art. It is notably described by Ashman (1999) *Int. J. Biochem. Cell. Biol.* 31:1037-1051. By way of example, the human

c-Kit receptor is encoded by SEQ ID NO: 8. Accordingly, it is well within the reach of the man skilled in the art to identify, design or select ligands of the c-Kit receptor.

The natural ligand of the c-Kit receptor is the Stem Cell Factor (SCF) cytokine. The SCF cytokine is notably described by Ashman (1999) *Int. J. Biochem. Cell. Biol.* 31:1037-1051. As such, in the above-defined vector particle, the ligand of the c-Kit receptor is preferably the SCF cytokine. As intended herein the expression SCF cytokine relates to a natural SCF cytokine or to any mutant of a natural SCF cytokine derived from said natural SCF by deletion, insertion or substitution of one or several amino acids, wherein said mutant retains the ability of the natural SCF cytokine to bind to the c-Kit receptor. Preferably, the SCF cytokine is the human SCF cytokine. By way of example the human SCF cytokine corresponds to GenBank reference number P21583. It is most preferred that the SCF cytokine used herein is deprived of its signal peptide and of its transmembrane and cytoplasmic domain (i.e. only the extracellular domain of the SCF cytokine is used), e.g. as represented by SEQ ID NO: 9.

More preferably, the second protein of the above-defined vector particle comprises or consists in a fusion of the SCF cytokine and (i) the N-terminal domain of an hemagglutinin glycoprotein, or (ii) a retroviral envelope glycoprotein. In this fusion it is preferred that the C-terminus of SCF is fused to the N-terminus of the N-terminal domain of the hemagglutinin glycoprotein or to the N-terminus of the retroviral envelope glycoprotein.

Preferably, the hemagglutinin glycoprotein is that of an influenza virus, more preferably of the Fowl Plague Virus.

Preferably, the N-terminal domain of the hemagglutinin glycoprotein comprises or consists in the contiguous amino acids from the N-terminus of the glycoprotein to the C-terminus of the HA1 subunit.

The subunit structure of the hemagglutinin glycoprotein is well known to one of skill in the art. The Fowl Plaque Virus hemagglutinin is notably described in Hatzioannou et al. (1998) *J. Virol.* 72:5313-5317.

By way of example the N-terminal domain of the Fowl Plague Virus hemagglutinin is represented by SEQ ID NO: 10.

Preferably, in the second protein, the retroviral envelope glycoprotein is Murine Leukemia Virus-A envelope glycoprotein.

As will be apparent to anyone of skill in the art, the second protein may also preferably comprise a signal peptide intended for promoting endoplasmic reticulum translocation of the second protein. In certain cases the signal peptide can be cleaved during or after insertion in the targeted membrane. Such signal peptides are well known to the man skilled in the art and can be found, for example, at the extremities of membrane proteins. By way of example the signal peptide can be that of the Murine Leukemia Virus-A envelope glycoprotein, which can be represented by SEQ ID NO: 7.

Thus, the second protein preferably comprises or consists in a fusion of the SCF cytokine, the N-terminal domain of an hemagglutinin glycoprotein, and a signal peptide. In this fusion it is preferred that the C-terminus of the signal peptide is fused to the N-terminus of SCF, and that the C-terminus of SCF is fused to the N-terminus of the N-terminal domain of the hemagglutinin glycoprotein.

When the second protein comprises or consists in a fusion of SCF and a retroviral envelope glycoprotein, it is preferred that the C-terminus of SCF is fused to the N-terminus of the retroviral envelope glycoprotein deprived of its signal peptide, and that the N-terminus of SCF is fused to the C-terminus

nus of a signal peptide as defined above, which is preferably the signal peptide of the retroviral envelope glycoprotein to which it is fused.

Most preferably, the second protein is represented by SEQ ID NO: 4 and is in particular encoded by SEQ ID NO: 3. A preferred plasmid for expressing the first protein in a producer cell is represented by SEQ ID NO: 12.

In a particular embodiment of the above-defined vector particle, the first protein is represented by SEQ ID NO: 2 and the second protein is represented by SEQ ID NO: 4.

In another particular embodiment, the second protein as defined above is fused to the first protein as defined above. Preferably, when the first and second proteins are fused, the second protein consists of a SCF cytokine, optionally fused to a signal peptide as defined above. More preferably, when the first and second protein are fused, the C-terminus of a signal peptide is fused to the N-terminus of a SCF cytokine, the C-terminus of the SCF cytokine is fused to the N-terminus of the extracellular domain of RD114, and the C-terminus of the transmembrane domain of RD114 is fused to the N-terminus of the cytoplasmic domain of a retroviral envelope glycoprotein.

The present invention also relates to the fused first and second proteins as defined above and to the nucleic acids which comprise sequences encoding them.

In another particular embodiment, the above-defined vector particle does not comprise the Vesicular Stomatitis Virus (VSV) G envelope glycoprotein.

The VSV-G envelope glycoprotein is notably described in Yee et al. (1994) *Methods Cell Biol.* 43:99-112. By way of example the VSV-G envelope glycoprotein is represented by SEQ ID NO: 13.

As is apparent from the foregoing, the above-defined vector particle can be used for the in vivo or ex vivo transfer of biological material to cells, in particular to CD34⁺ cells, and among them to HSCs.

Accordingly, the vector particle is particularly indicated for treating hematopoietic cells-related diseases either by direct administration of the vector particle to the individual afflicted by such a disease, or by administering cells, in particular cells originating from the individual afflicted by such a disease, which have been contacted ex vivo with the vector particle.

In this frame, it is preferred that the vector particle is a lentiviral vector particle as defined above and/or that the target cells are transduced by one or more nucleic acids, preferably intended for treating the disease.

The vector particle would thus be indicated for treating myelosuppression and neutropenias which may be caused as a result of chemotherapy, immunosuppressive therapy, infections such as AIDS, genetic disorders of hematopoietic cells, cancers and the like.

Exemplary genetic disorders of hematopoietic cells that are contemplated include sickle cell anemia, thalassemias, hemoglobinopathies, Glanzmann thrombasthenia, lysosomal storage disorders (such as Fabry disease, Gaucher disease, Niemann-Pick disease, and Wiskott-Aldrich syndrome), severe combined immunodeficiency syndromes (SCID), as well as diseases resulting from the lack of systemic production of a secreted protein, for example, coagulation factor VIII and/or IX.

In such cases, one would desire to transfer one or more nucleic acids such as globin genes, hematopoietic growth factors, which include erythropoietin (EPO), the interleukins (especially Interleukin-1, Interleukin-2, Interleukin-3, Interleukin-6, Interleukin-12, etc.) and the colony-stimulating factors (such as granulocyte colony-stimulating factor, granulo-

cyte/macrophage colony-stimulating factor, or stem-cell colony-stimulating factor), the platelet-specific integrin $\alpha\text{IIb}\beta$, multidrug resistance genes, the gp91 or gp 47 genes which are defective in patients with chronic granulomatous disease (CGD), antiviral genes rendering cells resistant to infections with pathogens such as human immunodeficiency virus, genes coding for blood coagulation factors VIII or IX which are mutated in hemophiliacs, ligands involved in T cell-mediated immune responses such as T cell antigen receptors, B cell antigen receptors (immunoglobulins), the interleukin receptor common γ chain, a combination of both T and B cell antigen receptors alone and/or in combination with single chain antibodies (ScFv), IL2, IL12, TNF, gamma interferon, CTLA4, B7 and the like, genes expressed in tumor cells such as Melana, MAGE genes (such as MAGE-1, MAGE-3), P198, P1A, gp100 etc.

Exemplary cancers are those of hematopoietic origin, for example, arising from myeloid, lymphoid or erythroid lineages, or precursor cells thereof. Exemplary myeloid disorders include, but are not limited to, acute promyeloid leukemia (APML), acute myelogenous leukemia (AML) and chronic myelogenous leukemia (CML), Lymphoid malignancies which may be treated using a vector particle as defined above include, but are not limited to acute lymphoblastic leukemia (ALL) which includes B-lineage ALL and T-lineage ALL, chronic lymphocytic leukemia (CLL), prolymphocytic leukemia (PLL), hairy cell leukemia (HLL) and Waldenstrom's macroglobulinemia (WM). Additional forms of malignant lymphomas contemplated as candidates for treatment utilizing the lentiviral vector particles of the present invention include, but are not limited to non-Hodgkin lymphoma and variants thereof, peripheral T-cell lymphomas, adult T-cell leukemia/lymphoma (ATL), cutaneous T-cell lymphoma (CTCL), large granular lymphocytic leukemia (LGF) and Hodgkin's disease.

Where the vector particle is used as a medicament and is administered to an individual in a therapeutic method, administration through the intravenous route or by the medullar route, in particular the femur or humerus medullar route, is preferred. For intravenous administration a unit dose from about $5 \cdot 10^8$ to about 10^9 vector particles as defined above can be used, whereas for medullar administration a unit dose from about 10^8 to about $5 \cdot 10^8$ vector particles as defined above can be used.

Where the vector particle is used ex vivo the vector particle can be contacted, preferably in vitro, either with isolated or purified cells, such as CD34⁺ cells, or with non-purified bodily samples.

The cells can be isolated or purified from various tissues, in particular taken from the individual, such as blood, in particular cord blood, or bone marrow.

Non-purified bodily samples can originate from the individual to be treated, and notably comprise blood samples, in particular whole cord blood samples.

The quantity of vector particle to be used for ex vivo transfers of biological material is for example from about 10^7 to about $5 \cdot 10^7$ for about 10^6 total white blood cells (where the cells to be transduced are comprised in total white blood cells from a whole blood sample).

EXAMPLES

Example 1

Production of Lentiviral Vector Particles (LVs)

The inventors displayed two early acting cytokines, Thrombopoietin (TPO) and Stem Cell Factor (SCF), on a lentiviral vector particle (LV) surface.

A TPO truncated form of 171-amino acid long, shown to have a 3-fold higher biological activity than wild-type TPO, was fused to the N-terminus of the influenza hemagglutinin (HA) glycoprotein to form TPOHA. The second cytokine, SCF, was also fused to the N-terminus of HA glycoprotein to form SCFHA (SEQ ID NO: 4), which efficiently incorporates on LVs.

Since these chimeric HA glycoproteins demonstrated a reduced infectivity, an additional fusion competent glycoprotein was co-expressed. A chimeric feline endogenous RD114 virus envelope glycoprotein was chosen, in which the cytoplasmic tail of RD114 was exchanged for that of Murine Leukemia Virus-A (MLV-A) env glycoprotein resulting in a mutant RDTR (SEQ ID NO: 2), that allows high incorporation onto HIV as well as SIV vector particles (Sandrin et al. (2002) *Blood* 100:823-832).

Thus, a transfection protocol was optimized to co-display SCFHA or TPOHA with RDTR on HIV-derived lentiviral vector particles.

Briefly, $2.5 \cdot 10^6$ 293T cells were seeded the day before transfection in 10 cm plates in a final volume of 10 ml DMEM. The next day these cells were cotransfected with an HIV or SIV gag-pol construct (8.6 μ g) with the lentiviral gene transfer vector particle (8.6 μ g) and two glycoprotein-encoding constructs selected from: a) VSV-G (1.5 μ g) (SEQ ID NO: 14) or RDTR (SEQ ID NO: 11) (7 μ g) and b) TPOHA (SEQ ID NO: 15) or c) SCFHA (SEQ ID NO: 12) (1.5 μ g), using the Clontech calcium-phosphate transfection system. 4 μ g of a neuraminidase-encoding plasmid was also co-transfected to allow efficient release of vector particle from the producer cell since the HA (SCFHA and TPOHA) envelope otherwise binds the vector particles to the producer cells because of the expression of sialic acid by the producer 293T cells. 15 h after transfection, the medium was replaced with 6 ml of fresh CellGro® medium (CellGenix) and 36 h after transfection, vector particles were harvested, filtrated through 0.45 μ m pore-sized membrane and stored at -80° C. The vector particles can be further concentrated via ultracentrifugation or polyethylene-glycol mediated concentration at low-speed centrifugation.

Titers of $5 \cdot 10^5$ - 10^6 IU/ml were thus obtained, that were comparable to RDTR single pseudotyped vector particles.

Functional co-display of TPO on TPOHA/RDTR co-displaying vector particles was demonstrated on BAF3-Mpl cells, which are dependent on TPO for survival and growth, essentially as described by Geddis et al. (2001) *J. Biol. Chem.* 276:34473-34479. Similarly, functional co-display of SCF on SCFHA/RDTR vector particles was confirmed since they sustained survival of BAF3-cKit cells which depend on SCF for survival (Bayle et al. (2004) *J Biol Chem.* 279:12249-12259), even at low multiplicity of infection (M.O.I.)

Example 2

Transduction of Isolated CD34⁺ Cells

The vector particles were first tested on the transduction of CD34⁺ cells isolated from human cord blood (CB). CB CD34⁺ cells are very immature hematopoietic cells containing hematopoietic stem cells.

Briefly, CD34⁺ cells were isolated by positive selection using anti-CD34⁺ beads (Miltenyi Biotech) from cord blood and were cultured on uncoated or RetroNectin® (Takara) coated plates. Subsequently, the cells were incubated with Green Fluorescent Protein (GFP) encoding HIV derived vector particles displaying RDTR, in the presence of human recombinant cytokines (TPO=10 ng/ml; SCF=50 ng/ml)

(Preprotech, Rocky Hill, US), or co-displaying RDTR and TPOHA or RDTR and SCFHA, at a multiplicity of infection (M.O.I.) of 10, essentially as described by Verhoeyen et al. (2005) *Blood* 106:3386-3395.

As shown in FIG. 1, the resulting RDTR/SCFHA pseudotyped HIV vector particles were far more efficient in transducing cord blood-derived CD34⁺ cells, than the LV pseudotyped with RDTR and TPOHA, or with RDTR only in the presence of the corresponding cytokines in their soluble form. In addition, in contrast to the RDTR/SCFHA pseudotyped HIV vector particles, the RDTR-only pseudotyped vector particles are completely dependent on RetroNectin® for the transduction of CD34⁺ cells (RetroNectin® is a chimeric peptide of human fibronectin produced in *Escherichia coli* which is thought to link vector particles and target cells).

Thus, the above results indicate that an unexpected synergistic mechanism is taking place, between RDTR, allowing vector particle and cell fusion, and SCFHA, allowing specific binding and stimulation of c-Kit⁺/CD34⁺ cells, which results in the high transduction efficiency observed.

Example 3

Multiplicity of Infection for CD34⁺ Cells

An important issue for the in vivo use of the vector particles of the invention is that they should allow high transduction efficiency into CD34⁺ cells even at very low vector particle dosage, since a systemic administration of a therapeutic vector particle would result in an important dilution of vector particle concentration. Thus, the inventors tested the minimal effective dosage of the vector particles according to the invention.

Briefly, CD34⁺ cells were isolated by positive selection using anti-CD34⁺ beads (Miltenyi Biotech) from cord blood and were cultured on uncoated culture plates (i.e. in the absence of RetroNectin®). Subsequently, the cells were incubated with Green Fluorescent Protein (GFP) encoding HIV derived vector particles displaying RDTR, in the presence of human recombinant cytokines (TPO=10 ng/ml; SCF=50 ng/ml), or co-displaying RDTR and TPOHA or RDTR and SCFHA at a M.O.I. of 10, 2, or 0.2, essentially as described by Verhoeyen et al. (2005) *Blood* 106:3386-3395. At day 3 post initiation of transduction, cells were evaluated for GFP expression by fluorescence-activated cell sorter (FACS).

As shown in FIG. 2, the RDTR/SCFHA vector particle of the invention enabled a reduction of vector particle dosage to a M.O.I. of 0.2, without observing a significant drop in transduction efficiency of CD34⁺ cells. Thus, a 50-fold decrease in RDTR/SCFHA vector particle dosage resulted on average only in a 1.4-fold reduction of CD34⁺ cell transduction. In contrast, the RDTR/TPOHA vector particle resulted in a significantly lower CD34⁺ transduction when an M.O.I. of 0.2 was used.

Example 4

RDTR/SCFHA Targets Transduction to CD34⁺ Cells in a Peripheral Mononuclear Blood Cell Population

A vector particle intended for in vivo gene therapy notably needs to be highly discriminative between target and non-target cells. Thus, after having demonstrated the ability of the vector particle according to the invention to transduce isolated CD34⁺ cells, its selectivity was evaluated by adding vector particle to a whole peripheral blood mononuclear cell

(PBMC) population at low M.O.I. In this respect, it is important to highlight that no more than 1% CD34⁺ cells are contained in such a population.

Briefly, PBMCs were isolated from fresh cord blood by ficol gradient, as is well-known to the man skilled in the art, and cultured in the absence of RetroNectin®. Transduction of PBMCs was performed with Green Fluorescent Protein (GFP) encoding HIV derived vector particles displaying RDTR or VSV-G in the presence of human rSCF (50 ng/ml), or co-displaying RDTR and SCFHA or VSV-G and SCFHA, without adding exogenous cytokines, at a M.O.I. of 0.2, essentially as described by Verhoeven et al. (2005) *Blood* 106:3386-3395. At day 3 post initiation of transduction, CD34⁺ and CD3⁺ cells were evaluated for GFP expression by fluorescence-activated cell sorter (FACS).

As shown in FIG. 3, the RDTR/SCFHA vector particle was able to preferentially target and transduce CD34⁺ target cells (up to 19%), in sharp contrast to the vector particle pseudotyped with RDTR only, in the presence of soluble SCF, which provided for no transduction at all, or to the VSV-G/SCFHA vector particle, which allowed a transduction level of CD34⁺ cells of 5% at the most. Importantly, the RDTR/SCFHA vector particle allowed to transduce CD34⁺ cells within the PBMC population at a level equivalent to that obtained for the transduction of isolated CD34⁺ cells (compare FIGS. 2 and 3). Furthermore, the T-cell population, which make up 80% of the whole PBMC population, was very poorly transduced by the RDTR/SCFHA vector particle (FIG. 3). Worth noting, other cell lineages present in the PBMC population, such as monocytes, B-cells and NK-cells were not transduced at all.

Example 5

RDTR/SCFHA Targets Transduction to CD34⁺ Cells in In Vivo-Like Conditions

The inventors then devised conditions as close as possible to in vivo settings for targeting gene transfer into CD34⁺ cells. Thus, the inventors performed transduction of fresh total cord blood, which contains cells from each hematopoietic lineage: early progenitors, including Hematopoietic Stem Cells (HSGs), lymphocytes, monocytes, and erythrocytes. This allows, (i) evaluation of targeted gene transfer in the CD34⁺ cells population, which represents only 0.001% of cells in whole blood, and (ii) exposure of the vector particle to an active human complement system, an obstacle encountered by viral vector particles in vivo.

Thus, fresh total cord blood (0.5 ml) was incubated with GFP encoding HIV vector particles pseudotyped with RDTR only or VSV-G only, in the presence of soluble SCF (50 ng/ml), or co-displaying RDTR and SCFHA or VSV-G and SCFHA, without adding exogenous cytokines, at a M.O.I. of 0.01 (calculated for the total amount of white and red blood cells present in the blood sample). After 6-8 h incubation with the vector particles, total PBMCs were separated from the blood by a ficol gradient.

Subsequently, the CD34⁺ cells were isolated by positive selection using anti-CD34⁺ beads (Miltenyi Biotech) and were further cultured in a serum-free medium in presence of soluble recombinant human SCF in order to sustain survival until FACS analysis.

In order to reveal possible non-target gene transfer, after removal of the CD34⁺ cells, the residual PBMCs, consisting mainly of T-cells, were cultured in RPMI supplemented with anti-CD3 and anti-CD28 antibodies (BD Pharmingen, Le Pont de Claix, France) and recombinant human IL-2 (Preprotech Rocky Hill, US). This was done with a dual purpose: (i)

to activate T-cells in order to enable transduction, since the majority of T-cells in the blood are in a quiescent state and accordingly are not permissive to lentiviral transduction, and (ii) to sustain survival of these cells until analysis. Worth noting, very stringent conditions were thus used to reveal gene transfer in the non-target T-cell, which are most probably never met in in vivo conditions. In other words the experimental settings used most probably overestimate in vivo non-specific gene transduction of T-cell. At day 4 post initiation of transduction, CD34⁺ and CD3⁺ cells were evaluated for GFP expression by fluorescence-activated cell sorter (FACS).

As shown in FIG. 4, the RDTR/SCFHA vector particle allowed a transduction of 4.5% CD34⁺ cells versus 0.4% for the VSV-G/SCFHA vector particle, while transduction with vector particles displaying VSV-G only or RDTR only is negligible. Thus, the RDTR/SCFHA vector particle is 10 times more efficient than the VSV-G/SCFHA vector particle for transducing CD34⁺ cells. In addition, the VSV-G/SCFHA vector particle readily transduced the non-target T-cell population, resulting in an 1.8 fold only selectivity for CD34⁺ cells transduction as compared to T-cell. In contrast, the RDTR vector particle demonstrates up to 95-fold selectivity for CD34⁺ cells as compared to T-cells. Thus, knowing that only 0.01% of the blood cells initially transduced are CD34⁺ cells and that T-cells represent 1% of the blood cells, the RDTR/SCFHA vector particles efficiently target transduction to CD34⁺ cells.

As regards the low transduction efficiency achieved with the VSV-G/SCFHA vector particles, it might be due to the vector's susceptibility to human complement, which, as a consequence, would impair its use in vivo.

Example 6

RDTR/SCFHA Displaying LVs Allow Gene Transfer into hCD34⁺ Cells In Vivo

The inventors assessed targeted gene transfer into HSCs by the RDTR/SCFHA vector particles in vivo in a humanized murine model.

Briefly, full and functional reconstitution of all human haematopoietic lineages including B and T-cells was achieved in newborn Rag2^{-/-}; γ c^{-/-} Balbc mice by injection with human umbilical cord blood (UCB) CD34⁺ cells. After 13 weeks of reconstitution the inventors detected on average 35% of human cells (hCD45⁺) in the bone marrow of these mice (FIG. 5) of which 5 to 15% expressed hCD34.

GFP-encoding RDTR/SCFHA vector particles were concentrated by low speed centrifugation over a filtration column to obtain titers up to 5·10⁸ IU/ml. 1·10⁵ infectious units of the RDTR/SCFHA vector particles were injected into the femoral bone marrow of the humanized mice from 13 week of age on.

One week after the injection, three-colour marking was performed to measure GFP expression in the different haematopoietic lineages as well as in the target hCD34⁺ cells in the bone marrow.

In the flushed bone marrow the inventors detected a transduction of up to 3% of the total human cells that had colonized the marrow of the mice (FIG. 5). Taking into account that a femur contains 1.5·10⁷ cells, the inventors administered a very low vector dose (MOI=0.006). However, a selective transduction of up to 3% of early human progenitors (hCD34⁺ cells) and of 3% of the myeloid progenitors (hCD13⁺) in the BM was detected (FIG. 6). In contrast, monocytes and pre- and pro-B-cells were transduced to a low extent (hCD14=0%;

hCD19=0.2%). These results should be explained by the fact, that one week after the injection, differentiation of hCD34⁺ cells, including transduced hCD34⁺ cells, into early progenitors such as hCD13⁺ myeloid progenitors and pre- and pro-B cells may have already occurred.

Of utmost importance, the inventors verified in vivo escape of vectors by analysing transduction of the other hematopoietic tissues. They did not detect GFP⁺ human thymocytes (FIG. 7), nor transduction of human CD19⁺ B-cells and CD3⁺ T-cells in the blood stream of these intrafemoral injected mice (FIG. 8). Additionally, they did not detect significant levels of transduced B-cells (hCD19⁺ cells) and transduced T-cells in the spleen (FIG. 9).

Summarizing, local administration of low doses of RDTR/SCFHA LV into the BM of humanized mice resulted in a selective transduction of hCD34⁺ cells in vivo.

Sequence Identifiers Reference Table:

SEQ ID NO:	Feature
1	Nucleic acid encoding a fusion of the transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein and the cytoplasmic domain of MLV-A envelope glycoprotein

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SEQ ID NO:	Feature
2	Fusion of the transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein and the cytoplasmic domain of MLV-A envelope glycoprotein
3	Nucleic acid encoding a fusion of the SCF cytokine, the N-terminal domain of an influenza virus hemagglutinin glycoprotein, and a signal peptide
4	Fusion of the SCF cytokine, the N-terminal domain of an influenza virus hemagglutinin glycoprotein, and a signal peptide
5	Transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein
6	Cytoplasmic domain of Murine Leukemia Virus-A envelope glycoprotein
7	Signal peptide of the Murine Leukemia Virus-A envelope glycoprotein
8	Human c-Kit receptor
9	Human SCF cytokine
10	N-terminal domain of the Fowl Plague Virus hemagglutinin
11	Plasmid encoding the fusion protein of SEQ ID NO: 2
12	Plasmid encoding the fusion protein of SEQ ID NO: 4
13	VSV-G envelope glycoprotein
14	Plasmid encoding VSV-G
15	Plasmid encoding TPOHA

SEQUENCE LISTING

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<223> OTHER INFORMATION: Fusion of the transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein and the cytoplasmic domain of MLV-A envelope glycoprotein

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<223> OTHER INFORMATION: Fusion of the transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein and the cytoplasmic domain of MLV-A envelope glycoprotein

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545					550					555					560
Tyr	Glu	Pro													

<210> SEQ ID NO 3

<211> LENGTH: 2385

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

-continued

<223> OTHER INFORMATION: Fusion of the SCF cytokine, the N-terminal domain of an influenza virus hemagglutinin glycoprotein, and a signal peptide

<220> FEATURE:

<221> NAME/KEY: CDS

<222> LOCATION: (1)..(2385)

<400> SEQUENCE: 3

atg gcg cgt tca acg ctc tca aaa ccc ctt aaa aat aag gtt aac ccg	48
Met Ala Arg Ser Thr Leu Ser Lys Pro Leu Lys Asn Lys Val Asn Pro	
1 5 10 15	
cga ggc ccc cta atc ccc tta att ctt ctg atg ctc aga ggg gtc agt	96
Arg Gly Pro Leu Ile Pro Leu Ile Leu Leu Met Leu Arg Gly Val Ser	
20 25 30	
act gct tcg ccc ggc tcc agt gcg gcc cag ccg gcc gaa ggg atc tgc	144
Thr Ala Ser Pro Gly Ser Ser Ala Ala Gln Pro Ala Glu Gly Ile Cys	
35 40 45	
agg aat cgt gtg act aat aat gta aaa gac gtc act aaa ttg gtg gca	192
Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr Lys Leu Val Ala	
50 55 60	
aat ctt cca aaa gac tac atg ata acc ctc aaa tat gtc ccc ggg atg	240
Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr Val Pro Gly Met	
65 70 75 80	
gat gtt ttg cca agt cat tgt tgg ata agc gag atg gta gta caa ttg	288
Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met Val Val Gln Leu	
85 90 95	
tca gac agc ttg act gat ctt ctg gac aag ttt tca aat att tct gaa	336
Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser Asn Ile Ser Glu	
100 105 110	
ggc ttg agt aat tat tcc atc ata gac aaa ctt gtg aat ata gtc gat	384
Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val Asn Ile Val Asp	
115 120 125	
gac ctt gtg gag tgc gtc aaa gaa aac tca tct aag gat cta aaa aaa	432
Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys Asp Leu Lys Lys	
130 135 140	
tca ttc aag agc cca gaa ccc agg ctc ttt act cct gaa gaa ttc ttt	480
Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro Glu Glu Phe Phe	
145 150 155 160	
aga att ttt aat aga tcc att gat gcc ttc aag gac ttt gta gtg gca	528
Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp Phe Val Val Ala	
165 170 175	
tct gaa act agt gat tgt gtg gtt tct tca aca tta agt cct gag aaa	576
Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu Ser Pro Glu Lys	
180 185 190	
gat tcc aga gtc agt gtc aca aaa cca ttt atg tta ccc cct gtt gca	624
Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu Pro Pro Val Ala	
195 200 205	
gcc agc tcc ctt agg aat gac agc agt agc agt aat agg aag gcc aaa	672
Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn Arg Lys Ala Lys	
210 215 220	
aat ccc cct gga gac tcc agc cta cac gcg gcc gca atc gag gga agg	720
Asn Pro Pro Gly Asp Ser Ser Leu His Ala Ala Ala Ile Glu Gly Arg	
225 230 235 240	
caa gac ctt cca gga aat gac aac agc gac aaa att tgt ctt gga cat	768
Gln Asp Leu Pro Gly Asn Asp Asn Ser Asp Lys Ile Cys Leu Gly His	
245 250 255	
cat gct gta tca aat ggc acc aaa gta aac aca ctc act gag aga gga	816
His Ala Val Ser Asn Gly Thr Lys Val Asn Thr Leu Thr Glu Arg Gly	
260 265 270	
gta gaa gtt gtc aat gca acg gaa aca gtg gag cgg aca aac atc ccc	864
Val Glu Val Val Asn Ala Thr Glu Thr Val Glu Arg Thr Asn Ile Pro	
275 280 285	

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aaa att tgc tca aaa ggg aaa aga acc act gat ctt ggc caa tgc gga	912
Lys Ile Cys Ser Lys Gly Lys Arg Thr Thr Asp Leu Gly Gln Cys Gly	
290 295 300	
ctg tta ggg acc att acc gga cca cct caa tgc gac caa ttt cta gaa	960
Leu Leu Gly Thr Ile Thr Gly Pro Pro Gln Cys Asp Gln Phe Leu Glu	
305 310 315 320	
ttt tca gct gat cta ata atc gag aga cga gaa gga aat gat gtt tgt	1008
Phe Ser Ala Asp Leu Ile Ile Glu Arg Arg Glu Gly Asn Asp Val Cys	
325 330 335	
tac ccg ggg aag ttt gtt aat gaa gag gca ttg cga caa atc ctc aga	1056
Tyr Pro Gly Lys Phe Val Asn Glu Glu Ala Leu Arg Gln Ile Leu Arg	
340 345 350	
gga tca ggt ggg att gac aaa gaa aca atg gga ttc aca tat agt gga	1104
Gly Ser Gly Gly Ile Asp Lys Glu Thr Met Gly Phe Thr Tyr Ser Gly	
355 360 365	
ata agg acc aac gga aca act agt gca tgt aga aga tca ggg tct tca	1152
Ile Arg Thr Asn Gly Thr Thr Ser Ala Cys Arg Arg Ser Gly Ser Ser	
370 375 380	
ttc tat gca gaa atg gag tgg ctc ctg tca aat aca gac aat gct tct	1200
Phe Tyr Ala Glu Met Glu Trp Leu Leu Ser Asn Thr Asp Asn Ala Ser	
385 390 395 400	
ttc cca caa atg aca aaa tca tac aaa aac aca agg aga gaa tca gct	1248
Phe Pro Gln Met Thr Lys Ser Tyr Lys Asn Thr Arg Arg Glu Ser Ala	
405 410 415	
ctg ata gta tgg gga atc cac cat tca gga tca acc acc gaa cag acc	1296
Leu Ile Val Trp Gly Ile His His Ser Gly Ser Thr Thr Glu Gln Thr	
420 425 430	
aaa cta tat ggg agt gga aat aaa ctg ata aca gtc ggg agt tcc aaa	1344
Lys Leu Tyr Gly Ser Gly Asn Lys Leu Ile Thr Val Gly Ser Ser Lys	
435 440 445	
tat cat caa tct ttt gtg ccg agt cca gga aca cga ccg cag ata aat	1392
Tyr His Gln Ser Phe Val Pro Ser Pro Gly Thr Arg Pro Gln Ile Asn	
450 455 460	
ggc cag tcc gga cgg att gat ttt cat tgg ttg atc ttg gat ccc aat	1440
Gly Gln Ser Gly Arg Ile Asp Phe His Trp Leu Ile Leu Asp Pro Asn	
465 470 475 480	
gat aca gtt act ttt agt ttc aat ggg gct ttc ata gct cca aat cgt	1488
Asp Thr Val Thr Phe Ser Phe Asn Gly Ala Phe Ile Ala Pro Asn Arg	
485 490 495	
gcc agc ttc ttg agg gga aag tcc atg ggg atc cag agc gat gtg cag	1536
Ala Ser Phe Leu Arg Gly Lys Ser Met Gly Ile Gln Ser Asp Val Gln	
500 505 510	
gtt gat gcc aat tgc gaa ggg gaa tgc tac cac agt gga ggg act ata	1584
Val Asp Ala Asn Cys Glu Gly Glu Cys Tyr His Ser Gly Gly Thr Ile	
515 520 525	
aca agc aga ttg cct ttt caa aac atc aat agc aga gca gtt ggc aaa	1632
Thr Ser Arg Leu Pro Phe Gln Asn Ile Asn Ser Arg Ala Val Gly Lys	
530 535 540	
tgc cca aga tat gta aaa cag gaa agt tta tta ttg gca act ggg atg	1680
Cys Pro Arg Tyr Val Lys Gln Glu Ser Leu Leu Leu Ala Thr Gly Met	
545 550 555 560	
aag aac gtt ccc gaa cct tcc aaa aaa agg aaa aaa aga ggc ctg ttt	1728
Lys Asn Val Pro Glu Pro Ser Lys Lys Arg Lys Lys Arg Gly Leu Phe	
565 570 575	
ggc gct ata gca ggg ttt att gaa aat ggt tgg gaa ggt ctg gtc gac	1776
Gly Ala Ile Ala Gly Phe Ile Glu Asn Gly Trp Glu Gly Leu Val Asp	
580 585 590	
ggg tgg tac ggt ttc agg cat cag aat gca caa gga gaa gga act gca	1824
Gly Trp Tyr Gly Phe Arg His Gln Asn Ala Gln Gly Glu Gly Thr Ala	
595 600 605	

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gca gac tac aaa agc acc caa tcg gca att gat cag ata acc gga aag 1872
 Ala Asp Tyr Lys Ser Thr Gln Ser Ala Ile Asp Gln Ile Thr Gly Lys
 610 615 620

 tta aat aga ctc att gag aaa acc aac cag caa ttt gag cta ata gat 1920
 Leu Asn Arg Leu Ile Glu Lys Thr Asn Gln Gln Phe Glu Leu Ile Asp
 625 630 635 640

 aat gaa ttc act gag gtg gaa aag cag att ggc aat tta att aac tgg 1968
 Asn Glu Phe Thr Glu Val Glu Lys Gln Ile Gly Asn Leu Ile Asn Trp
 645 650 655

 acc aaa gac tcc atc aca gaa gta tgg tct tac aat gct gaa ctt att 2016
 Thr Lys Asp Ser Ile Thr Glu Val Trp Ser Tyr Asn Ala Glu Leu Ile
 660 665 670

 gtg gca atg gaa aac cag cac act att gat ttg gct gat tca gag atg 2064
 Val Ala Met Glu Asn Gln His Thr Ile Asp Leu Ala Asp Ser Glu Met
 675 680 685

 aac agg ctg tat gag cga gtg agg aaa caa tta agg gaa aat gct gaa 2112
 Asn Arg Leu Tyr Glu Arg Val Arg Lys Gln Leu Arg Glu Asn Ala Glu
 690 695 700

 gag gat ggt act ggt tgc ttt gaa att ttt cat aaa tgt gac gat gat 2160
 Glu Asp Gly Thr Gly Cys Phe Glu Ile Phe His Lys Cys Asp Asp Asp
 705 710 715 720

 tgt atg gct agt ata agg aac aat act tat gat cac agc aaa tac aga 2208
 Cys Met Ala Ser Ile Arg Asn Asn Thr Tyr Asp His Ser Lys Tyr Arg
 725 730 735

 gaa gaa gcg atg caa aat aga ata caa att gac cca gtc aaa ttg agt 2256
 Glu Glu Ala Met Gln Asn Arg Ile Gln Ile Asp Pro Val Lys Leu Ser
 740 745 750

 agt ggc tac aaa gat gtg ata ctt tgg ttt agc ttc ggg gca tca tgc 2304
 Ser Gly Tyr Lys Asp Val Ile Leu Trp Phe Ser Phe Gly Ala Ser Cys
 755 760 765

 ttt ttg ctt ctt gcc att gca atg ggc ctt gtt ttc ata tgt gtg aag 2352
 Phe Leu Leu Leu Ala Ile Ala Met Gly Leu Val Phe Ile Cys Val Lys
 770 775 780

 aac gga aac atg cgg tgc act att tgt ata taa 2385
 Asn Gly Asn Met Arg Cys Thr Ile Cys Ile
 785 790

<210> SEQ ID NO 4

<211> LENGTH: 794

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Fusion of the SCF cytokine, the N-terminal
 domain of an influenza virus hemagglutinin glycoprotein, and a
 signal peptide

<400> SEQUENCE: 4

Met Ala Arg Ser Thr Leu Ser Lys Pro Leu Lys Asn Lys Val Asn Pro
 1 5 10 15

 Arg Gly Pro Leu Ile Pro Leu Ile Leu Leu Met Leu Arg Gly Val Ser
 20 25 30

 Thr Ala Ser Pro Gly Ser Ser Ala Ala Gln Pro Ala Glu Gly Ile Cys
 35 40 45

 Arg Asn Arg Val Thr Asn Asn Val Lys Asp Val Thr Lys Leu Val Ala
 50 55 60

 Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr Val Pro Gly Met
 65 70 75 80

 Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met Val Val Gln Leu
 85 90 95

 Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser Asn Ile Ser Glu

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100					105					110					
Gly	Leu	Ser	Asn	Tyr	Ser	Ile	Ile	Asp	Lys	Leu	Val	Asn	Ile	Val	Asp
	115						120					125			
Asp	Leu	Val	Glu	Cys	Val	Lys	Glu	Asn	Ser	Ser	Lys	Asp	Leu	Lys	Lys
	130					135					140				
Ser	Phe	Lys	Ser	Pro	Glu	Pro	Arg	Leu	Phe	Thr	Pro	Glu	Glu	Phe	Phe
145					150					155					160
Arg	Ile	Phe	Asn	Arg	Ser	Ile	Asp	Ala	Phe	Lys	Asp	Phe	Val	Val	Ala
			165						170					175	
Ser	Glu	Thr	Ser	Asp	Cys	Val	Val	Ser	Ser	Thr	Leu	Ser	Pro	Glu	Lys
			180					185					190		
Asp	Ser	Arg	Val	Ser	Val	Thr	Lys	Pro	Phe	Met	Leu	Pro	Pro	Val	Ala
		195					200					205			
Ala	Ser	Ser	Leu	Arg	Asn	Asp	Ser	Ser	Ser	Ser	Asn	Arg	Lys	Ala	Lys
	210					215					220				
Asn	Pro	Pro	Gly	Asp	Ser	Ser	Leu	His	Ala	Ala	Ala	Ile	Glu	Gly	Arg
225					230					235					240
Gln	Asp	Leu	Pro	Gly	Asn	Asp	Asn	Ser	Asp	Lys	Ile	Cys	Leu	Gly	His
				245					250					255	
His	Ala	Val	Ser	Asn	Gly	Thr	Lys	Val	Asn	Thr	Leu	Thr	Glu	Arg	Gly
			260					265					270		
Val	Glu	Val	Val	Asn	Ala	Thr	Glu	Thr	Val	Glu	Arg	Thr	Asn	Ile	Pro
		275					280					285			
Lys	Ile	Cys	Ser	Lys	Gly	Lys	Arg	Thr	Thr	Asp	Leu	Gly	Gln	Cys	Gly
	290					295					300				
Leu	Leu	Gly	Thr	Ile	Thr	Gly	Pro	Pro	Gln	Cys	Asp	Gln	Phe	Leu	Glu
305					310					315					320
Phe	Ser	Ala	Asp	Leu	Ile	Ile	Glu	Arg	Arg	Glu	Gly	Asn	Asp	Val	Cys
			325						330					335	
Tyr	Pro	Gly	Lys	Phe	Val	Asn	Glu	Glu	Ala	Leu	Arg	Gln	Ile	Leu	Arg
			340					345					350		
Gly	Ser	Gly	Gly	Ile	Asp	Lys	Glu	Thr	Met	Gly	Phe	Thr	Tyr	Ser	Gly
		355					360					365			
Ile	Arg	Thr	Asn	Gly	Thr	Thr	Ser	Ala	Cys	Arg	Arg	Ser	Gly	Ser	Ser
	370					375					380				
Phe	Tyr	Ala	Glu	Met	Glu	Trp	Leu	Leu	Ser	Asn	Thr	Asp	Asn	Ala	Ser
385					390					395					400
Phe	Pro	Gln	Met	Thr	Lys	Ser	Tyr	Lys	Asn	Thr	Arg	Arg	Glu	Ser	Ala
			405						410					415	
Leu	Ile	Val	Trp	Gly	Ile	His	His	Ser	Gly	Ser	Thr	Thr	Glu	Gln	Thr
			420					425					430		
Lys	Leu	Tyr	Gly	Ser	Gly	Asn	Lys	Leu	Ile	Thr	Val	Gly	Ser	Ser	Lys
		435					440					445			
Tyr	His	Gln	Ser	Phe	Val	Pro	Ser	Pro	Gly	Thr	Arg	Pro	Gln	Ile	Asn
	450					455					460				
Gly	Gln	Ser	Gly	Arg	Ile	Asp	Phe	His	Trp	Leu	Ile	Leu	Asp	Pro	Asn
465					470					475					480
Asp	Thr	Val	Thr	Phe	Ser	Phe	Asn	Gly	Ala	Phe	Ile	Ala	Pro	Asn	Arg
			485						490					495	
Ala	Ser	Phe	Leu	Arg	Gly	Lys	Ser	Met	Gly	Ile	Gln	Ser	Asp	Val	Gln
			500					505					510		
Val	Asp	Ala	Asn	Cys	Glu	Gly	Glu	Cys	Tyr	His	Ser	Gly	Gly	Thr	Ile
		515					520					525			

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Thr Ser Arg Leu Pro Phe Gln Asn Ile Asn Ser Arg Ala Val Gly Lys
 530 535 540
 Cys Pro Arg Tyr Val Lys Gln Glu Ser Leu Leu Leu Ala Thr Gly Met
 545 550 555 560
 Lys Asn Val Pro Glu Pro Ser Lys Lys Arg Lys Lys Arg Gly Leu Phe
 565 570 575
 Gly Ala Ile Ala Gly Phe Ile Glu Asn Gly Trp Glu Gly Leu Val Asp
 580 585 590
 Gly Trp Tyr Gly Phe Arg His Gln Asn Ala Gln Gly Glu Gly Thr Ala
 595 600 605
 Ala Asp Tyr Lys Ser Thr Gln Ser Ala Ile Asp Gln Ile Thr Gly Lys
 610 615 620
 Leu Asn Arg Leu Ile Glu Lys Thr Asn Gln Gln Phe Glu Leu Ile Asp
 625 630 635 640
 Asn Glu Phe Thr Glu Val Glu Lys Gln Ile Gly Asn Leu Ile Asn Trp
 645 650 655
 Thr Lys Asp Ser Ile Thr Glu Val Trp Ser Tyr Asn Ala Glu Leu Ile
 660 665 670
 Val Ala Met Glu Asn Gln His Thr Ile Asp Leu Ala Asp Ser Glu Met
 675 680 685
 Asn Arg Leu Tyr Glu Arg Val Arg Lys Gln Leu Arg Glu Asn Ala Glu
 690 695 700
 Glu Asp Gly Thr Gly Cys Phe Glu Ile Phe His Lys Cys Asp Asp Asp
 705 710 715 720
 Cys Met Ala Ser Ile Arg Asn Asn Thr Tyr Asp His Ser Lys Tyr Arg
 725 730 735
 Glu Glu Ala Met Gln Asn Arg Ile Gln Ile Asp Pro Val Lys Leu Ser
 740 745 750
 Ser Gly Tyr Lys Asp Val Ile Leu Trp Phe Ser Phe Gly Ala Ser Cys
 755 760 765
 Phe Leu Leu Leu Ala Ile Ala Met Gly Leu Val Phe Ile Cys Val Lys
 770 775 780
 Asn Gly Asn Met Arg Cys Thr Ile Cys Ile
 785 790

<210> SEQ ID NO 5

<211> LENGTH: 530

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein

<400> SEQUENCE: 5

Met Lys Leu Pro Thr Gly Met Val Ile Leu Cys Ser Leu Ile Ile Val
 1 5 10 15
 Arg Ala Gly Phe Asp Asp Pro Arg Lys Ala Ile Ala Leu Val Gln Lys
 20 25 30
 Gln His Gly Lys Pro Cys Glu Cys Ser Gly Gly Gln Val Ser Glu Ala
 35 40 45
 Pro Pro Asn Ser Ile Gln Gln Val Thr Cys Pro Gly Lys Thr Ala Tyr
 50 55 60
 Leu Met Thr Asn Gln Lys Trp Lys Cys Arg Val Thr Pro Lys Ile Ser
 65 70 75 80
 Pro Ser Gly Gly Glu Leu Gln Asn Cys Pro Cys Asn Thr Phe Gln Asp
 85 90 95

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Ser Met His Ser Ser Cys Tyr Thr Glu Tyr Arg Gln Cys Arg Arg Ile
 100 105 110
 Asn Lys Thr Tyr Tyr Thr Ala Thr Leu Leu Lys Ile Arg Ser Gly Ser
 115 120 125
 Leu Asn Glu Val Gln Ile Leu Gln Asn Pro Asn Gln Leu Leu Gln Ser
 130 135 140
 Pro Cys Arg Gly Ser Ile Asn Gln Pro Val Cys Trp Ser Ala Thr Ala
 145 150 155 160
 Pro Ile His Ile Ser Asp Gly Gly Gly Pro Leu Asp Thr Lys Arg Val
 165 170 175
 Trp Thr Val Gln Lys Arg Leu Glu Gln Ile His Lys Ala Met Thr Pro
 180 185 190
 Glu Leu Gln Tyr His Pro Leu Ala Leu Pro Lys Val Arg Asp Asp Leu
 195 200 205
 Ser Leu Asp Ala Arg Thr Phe Asp Ile Leu Asn Thr Thr Phe Arg Leu
 210 215 220
 Leu Gln Met Ser Asn Phe Ser Leu Ala Gln Asp Cys Trp Leu Cys Leu
 225 230 235 240
 Lys Leu Gly Thr Pro Thr Pro Leu Ala Ile Pro Thr Pro Ser Leu Thr
 245 250 255
 Tyr Ser Leu Ala Asp Ser Leu Ala Asn Ala Ser Cys Gln Ile Ile Pro
 260 265 270
 Pro Leu Leu Val Gln Pro Met Gln Phe Ser Asn Ser Ser Cys Leu Ser
 275 280 285
 Ser Pro Phe Ile Asn Asp Thr Glu Gln Ile Asp Leu Gly Ala Val Thr
 290 295 300
 Phe Thr Asn Cys Thr Ser Val Ala Asn Val Ser Ser Pro Leu Cys Ala
 305 310 315 320
 Leu Asn Gly Ser Val Phe Leu Cys Gly Asn Asn Met Ala Tyr Thr Tyr
 325 330 335
 Leu Pro Gln Asn Trp Thr Arg Leu Cys Val Gln Ala Ser Leu Leu Pro
 340 345 350
 Asp Ile Asp Ile Asn Pro Gly Asp Glu Pro Val Pro Ile Pro Ala Ile
 355 360 365
 Asp His Tyr Ile His Arg Pro Lys Arg Ala Val Gln Phe Ile Pro Leu
 370 375 380
 Leu Ala Gly Leu Gly Ile Thr Ala Ala Phe Thr Thr Gly Ala Thr Gly
 385 390 395 400
 Leu Gly Val Ser Val Thr Gln Tyr Thr Lys Leu Ser His Gln Leu Ile
 405 410 415
 Ser Asp Val Gln Val Leu Ser Gly Thr Ile Gln Asp Leu Gln Asp Gln
 420 425 430
 Val Asp Ser Leu Ala Glu Val Val Leu Gln Asn Arg Arg Gly Leu Asp
 435 440 445
 Leu Leu Thr Ala Glu Gln Gly Gly Ile Cys Leu Ala Leu Gln Glu Lys
 450 455 460
 Cys Cys Phe Tyr Ala Asn Lys Ser Gly Ile Val Arg Asn Lys Ile Arg
 465 470 475 480
 Thr Leu Gln Glu Glu Leu Gln Lys Arg Arg Glu Ser Leu Ala Ser Asn
 485 490 495
 Pro Leu Trp Thr Gly Leu Gln Gly Phe Leu Pro Tyr Leu Leu Pro Leu
 500 505 510
 Leu Gly Pro Leu Leu Thr Leu Leu Leu Ile Leu Thr Ile Gly Pro Cys
 515 520 525

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Val Phe
530

<210> SEQ ID NO 6
<211> LENGTH: 33
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Cytoplasmic domain of Murine Leukemia Virus-A
envelope glycoprotein

<400> SEQUENCE: 6

Asn Arg Leu Val Gln Phe Val Lys Asp Arg Ile Ser Val Val Gln Ala
1 5 10 15
Leu Val Leu Thr Gln Gln Tyr His Gln Leu Lys Pro Leu Glu Tyr Glu
20 25 30

Pro

<210> SEQ ID NO 7
<211> LENGTH: 39
<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Signal peptide of the Murine Leukemia Virus-A
envelope glycoprotein

<400> SEQUENCE: 7

Met Ala Arg Ser Thr Leu Ser Lys Pro Leu Lys Asn Lys Val Asn Pro
1 5 10 15
Arg Gly Pro Leu Ile Pro Leu Ile Leu Leu Met Leu Arg Gly Val Ser
20 25 30

Thr Ala Ser Pro Gly Ser Ser
35

<210> SEQ ID NO 8
<211> LENGTH: 976
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Met Arg Gly Ala Arg Gly Ala Trp Asp Phe Leu Cys Val Leu Leu Leu
1 5 10 15
Leu Leu Arg Val Gln Thr Gly Ser Ser Gln Pro Ser Val Ser Pro Gly
20 25 30
Glu Pro Ser Pro Pro Ser Ile His Pro Gly Lys Ser Asp Leu Ile Val
35 40 45
Arg Val Gly Asp Glu Ile Arg Leu Leu Cys Thr Asp Pro Gly Phe Val
50 55 60
Lys Trp Thr Phe Glu Ile Leu Asp Glu Thr Asn Glu Asn Lys Gln Asn
65 70 75 80
Glu Trp Ile Thr Glu Lys Ala Glu Ala Thr Asn Thr Gly Lys Tyr Thr
85 90 95
Cys Thr Asn Lys His Gly Leu Ser Asn Ser Ile Tyr Val Phe Val Arg
100 105 110
Asp Pro Ala Lys Leu Phe Leu Val Asp Arg Ser Leu Tyr Gly Lys Glu
115 120 125
Asp Asn Asp Thr Leu Val Arg Cys Pro Leu Thr Asp Pro Glu Val Thr
130 135 140
Asn Tyr Ser Leu Lys Gly Cys Gln Gly Lys Pro Leu Pro Lys Asp Leu
145 150 155 160

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Arg Phe Ile Pro Asp Pro Lys Ala Gly Ile Met Ile Lys Ser Val Lys
 165 170 175

Arg Ala Tyr His Arg Leu Cys Leu His Cys Ser Val Asp Gln Glu Gly
 180 185 190

Lys Ser Val Leu Ser Glu Lys Phe Ile Leu Lys Val Arg Pro Ala Phe
 195 200 205

Lys Ala Val Pro Val Val Ser Val Ser Lys Ala Ser Tyr Leu Leu Arg
 210 215 220

Glu Gly Glu Glu Phe Thr Val Thr Cys Thr Ile Lys Asp Val Ser Ser
 225 230 235 240

Ser Val Tyr Ser Thr Trp Lys Arg Glu Asn Ser Gln Thr Lys Leu Gln
 245 250 255

Glu Lys Tyr Asn Ser Trp His His Gly Asp Phe Asn Tyr Glu Arg Gln
 260 265 270

Ala Thr Leu Thr Ile Ser Ser Ala Arg Val Asn Asp Ser Gly Val Phe
 275 280 285

Met Cys Tyr Ala Asn Asn Thr Phe Gly Ser Ala Asn Val Thr Thr Thr
 290 295 300

Leu Glu Val Val Asp Lys Gly Phe Ile Asn Ile Phe Pro Met Ile Asn
 305 310 315 320

Thr Thr Val Phe Val Asn Asp Gly Glu Asn Val Asp Leu Ile Val Glu
 325 330 335

Tyr Glu Ala Phe Pro Lys Pro Glu His Gln Gln Trp Ile Tyr Met Asn
 340 345 350

Arg Thr Phe Thr Asp Lys Trp Glu Asp Tyr Pro Lys Ser Glu Asn Glu
 355 360 365

Ser Asn Ile Arg Tyr Val Ser Glu Leu His Leu Thr Arg Leu Lys Gly
 370 375 380

Thr Glu Gly Gly Thr Tyr Thr Phe Leu Val Ser Asn Ser Asp Val Asn
 385 390 395 400

Ala Ala Ile Ala Phe Asn Val Tyr Val Asn Thr Lys Pro Glu Ile Leu
 405 410 415

Thr Tyr Asp Arg Leu Val Asn Gly Met Leu Gln Cys Val Ala Ala Gly
 420 425 430

Phe Pro Glu Pro Thr Ile Asp Trp Tyr Phe Cys Pro Gly Thr Glu Gln
 435 440 445

Arg Cys Ser Ala Ser Val Leu Pro Val Asp Val Gln Thr Leu Asn Ser
 450 455 460

Ser Gly Pro Pro Phe Gly Lys Leu Val Val Gln Ser Ser Ile Asp Ser
 465 470 475 480

Ser Ala Phe Lys His Asn Gly Thr Val Glu Cys Lys Ala Tyr Asn Asp
 485 490 495

Val Gly Lys Thr Ser Ala Tyr Phe Asn Phe Ala Phe Lys Gly Asn Asn
 500 505 510

Lys Glu Gln Ile His Pro His Thr Leu Phe Thr Pro Leu Leu Ile Gly
 515 520 525

Phe Val Ile Val Ala Gly Met Met Cys Ile Ile Val Met Ile Leu Thr
 530 535 540

Tyr Lys Tyr Leu Gln Lys Pro Met Tyr Glu Val Gln Trp Lys Val Val
 545 550 555 560

Glu Glu Ile Asn Gly Asn Asn Tyr Val Tyr Ile Asp Pro Thr Gln Leu
 565 570 575

Pro Tyr Asp His Lys Trp Glu Phe Pro Arg Asn Arg Leu Ser Phe Gly

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580					585					590					
Lys	Thr	Leu	Gly	Ala	Gly	Ala	Phe	Gly	Lys	Val	Val	Glu	Ala	Thr	Ala
		595					600					605			
Tyr	Gly	Leu	Ile	Lys	Ser	Asp	Ala	Ala	Met	Thr	Val	Ala	Val	Lys	Met
	610					615					620				
Leu	Lys	Pro	Ser	Ala	His	Leu	Thr	Glu	Arg	Glu	Ala	Leu	Met	Ser	Glu
						630					635				640
Leu	Lys	Val	Leu	Ser	Tyr	Leu	Gly	Asn	His	Met	Asn	Ile	Val	Asn	Leu
				645					650					655	
Leu	Gly	Ala	Cys	Thr	Ile	Gly	Gly	Pro	Thr	Leu	Val	Ile	Thr	Glu	Tyr
			660					665						670	
Cys	Cys	Tyr	Gly	Asp	Leu	Leu	Asn	Phe	Leu	Arg	Arg	Lys	Arg	Asp	Ser
		675						680					685		
Phe	Ile	Cys	Ser	Lys	Gln	Glu	Asp	His	Ala	Glu	Ala	Ala	Leu	Tyr	Lys
	690						695					700			
Asn	Leu	Leu	His	Ser	Lys	Glu	Ser	Ser	Cys	Ser	Asp	Ser	Thr	Asn	Glu
	705					710					715				720
Tyr	Met	Asp	Met	Lys	Pro	Gly	Val	Ser	Tyr	Val	Val	Pro	Thr	Lys	Ala
				725					730					735	
Asp	Lys	Arg	Arg	Ser	Val	Arg	Ile	Gly	Ser	Tyr	Ile	Glu	Arg	Asp	Val
			740					745					750		
Thr	Pro	Ala	Ile	Met	Glu	Asp	Asp	Glu	Leu	Ala	Leu	Asp	Leu	Glu	Asp
		755					760					765			
Leu	Leu	Ser	Phe	Ser	Tyr	Gln	Val	Ala	Lys	Gly	Met	Ala	Phe	Leu	Ala
	770					775					780				
Ser	Lys	Asn	Cys	Ile	His	Arg	Asp	Leu	Ala	Ala	Arg	Asn	Ile	Leu	Leu
	785					790					795				800
Thr	His	Gly	Arg	Ile	Thr	Lys	Ile	Cys	Asp	Phe	Gly	Leu	Ala	Arg	Asp
				805					810					815	
Ile	Lys	Asn	Asp	Ser	Asn	Tyr	Val	Val	Lys	Gly	Asn	Ala	Arg	Leu	Pro
			820					825					830		
Val	Lys	Trp	Met	Ala	Pro	Glu	Ser	Ile	Phe	Asn	Cys	Val	Tyr	Thr	Phe
		835					840					845			
Glu	Ser	Asp	Val	Trp	Ser	Tyr	Gly	Ile	Phe	Leu	Trp	Glu	Leu	Phe	Ser
	850					855					860				
Leu	Gly	Ser	Ser	Pro	Tyr	Pro	Gly	Met	Pro	Val	Asp	Ser	Lys	Phe	Tyr
	865					870					875				880
Lys	Met	Ile	Lys	Glu	Gly	Phe	Arg	Met	Leu	Ser	Pro	Glu	His	Ala	Pro
				885					890					895	
Ala	Glu	Met	Tyr	Asp	Ile	Met	Lys	Thr	Cys	Trp	Asp	Ala	Asp	Pro	Leu
			900					905					910		
Lys	Arg	Pro	Thr	Phe	Lys	Gln	Ile	Val	Gln	Leu	Ile	Glu	Lys	Gln	Ile
		915					920					925			
Ser	Glu	Ser	Thr	Asn	His	Ile	Tyr	Ser	Asn	Leu	Ala	Asn	Cys	Ser	Pro
	930					935					940				
Asn	Arg	Gln	Lys	Pro	Val	Val	Asp	His	Ser	Val	Arg	Ile	Asn	Ser	Val
	945					950					955				960
Gly	Ser	Thr	Ala	Ser	Ser	Ser	Gln	Pro	Leu	Leu	Val	His	Asp	Asp	Val
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<210> SEQ ID NO 9

<211> LENGTH: 189

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

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 <223> OTHER INFORMATION: Extracellular domain of the human SCF cytokine

<400> SEQUENCE: 9

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 Lys Leu Val Ala Asn Leu Pro Lys Asp Tyr Met Ile Thr Leu Lys Tyr
 20 25 30
 Val Pro Gly Met Asp Val Leu Pro Ser His Cys Trp Ile Ser Glu Met
 35 40 45
 Val Val Gln Leu Ser Asp Ser Leu Thr Asp Leu Leu Asp Lys Phe Ser
 50 55 60
 Asn Ile Ser Glu Gly Leu Ser Asn Tyr Ser Ile Ile Asp Lys Leu Val
 65 70 75 80
 Asn Ile Val Asp Asp Leu Val Glu Cys Val Lys Glu Asn Ser Ser Lys
 85 90 95
 Asp Leu Lys Lys Ser Phe Lys Ser Pro Glu Pro Arg Leu Phe Thr Pro
 100 105 110
 Glu Glu Phe Phe Arg Ile Phe Asn Arg Ser Ile Asp Ala Phe Lys Asp
 115 120 125
 Phe Val Val Ala Ser Glu Thr Ser Asp Cys Val Val Ser Ser Thr Leu
 130 135 140
 Ser Pro Glu Lys Asp Ser Arg Val Ser Val Thr Lys Pro Phe Met Leu
 145 150 155 160
 Pro Pro Val Ala Ala Ser Ser Leu Arg Asn Asp Ser Ser Ser Ser Asn
 165 170 175
 Arg Lys Ala Lys Asn Pro Pro Gly Asp Ser Ser Leu His
 180 185

<210> SEQ ID NO 10

<211> LENGTH: 558

<212> TYPE: PRT

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: N-terminal domain of the Fowl Plague Virus hemagglutinin

<400> SEQUENCE: 10

Ile Glu Gly Arg Gln Asp Leu Pro Gly Asn Asp Asn Ser Asp Lys Ile
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 Cys Leu Gly His His Ala Val Ser Asn Gly Thr Lys Val Asn Thr Leu
 20 25 30
 Thr Glu Arg Gly Val Glu Val Val Asn Ala Thr Glu Thr Val Glu Arg
 35 40 45
 Thr Asn Ile Pro Lys Ile Cys Ser Lys Gly Lys Arg Thr Thr Asp Leu
 50 55 60
 Gly Gln Cys Gly Leu Leu Gly Thr Ile Thr Gly Pro Pro Gln Cys Asp
 65 70 75 80
 Gln Phe Leu Glu Phe Ser Ala Asp Leu Ile Ile Glu Arg Arg Glu Gly
 85 90 95
 Asn Asp Val Cys Tyr Pro Gly Lys Phe Val Asn Glu Glu Ala Leu Arg
 100 105 110
 Gln Ile Leu Arg Gly Ser Gly Gly Ile Asp Lys Glu Thr Met Gly Phe
 115 120 125
 Thr Tyr Ser Gly Ile Arg Thr Asn Gly Thr Thr Ser Ala Cys Arg Arg
 130 135 140
 Ser Gly Ser Ser Phe Tyr Ala Glu Met Glu Trp Leu Leu Ser Asn Thr
 145 150 155 160

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Asp Asn Ala Ser Phe Pro Gln Met Thr Lys Ser Tyr Lys Asn Thr Arg
 165 170 175
 Arg Glu Ser Ala Leu Ile Val Trp Gly Ile His His Ser Gly Ser Thr
 180 185 190
 Thr Glu Gln Thr Lys Leu Tyr Gly Ser Gly Asn Lys Leu Ile Thr Val
 195 200 205
 Gly Ser Ser Lys Tyr His Gln Ser Phe Val Pro Ser Pro Gly Thr Arg
 210 215 220
 Pro Gln Ile Asn Gly Gln Ser Gly Arg Ile Asp Phe His Trp Leu Ile
 225 230 235 240
 Leu Asp Pro Asn Asp Thr Val Thr Phe Ser Phe Asn Gly Ala Phe Ile
 245 250 255
 Ala Pro Asn Arg Ala Ser Phe Leu Arg Gly Lys Ser Met Gly Ile Gln
 260 265 270
 Ser Asp Val Gln Val Asp Ala Asn Cys Glu Gly Glu Cys Tyr His Ser
 275 280 285
 Gly Gly Thr Ile Thr Ser Arg Leu Pro Phe Gln Asn Ile Asn Ser Arg
 290 295 300
 Ala Val Gly Lys Cys Pro Arg Tyr Val Lys Gln Glu Ser Leu Leu Leu
 305 310 315 320
 Ala Thr Gly Met Lys Asn Val Pro Glu Pro Ser Lys Lys Arg Lys Lys
 325 330 335
 Arg Gly Leu Phe Gly Ala Ile Ala Gly Phe Ile Glu Asn Gly Trp Glu
 340 345 350
 Gly Leu Val Asp Gly Trp Tyr Gly Phe Arg His Gln Asn Ala Gln Gly
 355 360 365
 Glu Gly Thr Ala Ala Asp Tyr Lys Ser Thr Gln Ser Ala Ile Asp Gln
 370 375 380
 Ile Thr Gly Lys Leu Asn Arg Leu Ile Glu Lys Thr Asn Gln Gln Phe
 385 390 395 400
 Glu Leu Ile Asp Asn Glu Phe Thr Glu Val Glu Lys Gln Ile Gly Asn
 405 410 415
 Leu Ile Asn Trp Thr Lys Asp Ser Ile Thr Glu Val Trp Ser Tyr Asn
 420 425 430
 Ala Glu Leu Ile Val Ala Met Glu Asn Gln His Thr Ile Asp Leu Ala
 435 440 445
 Asp Ser Glu Met Asn Arg Leu Tyr Glu Arg Val Arg Lys Gln Leu Arg
 450 455 460
 Glu Asn Ala Glu Glu Asp Gly Thr Gly Cys Phe Glu Ile Phe His Lys
 465 470 475 480
 Cys Asp Asp Asp Cys Met Ala Ser Ile Arg Asn Asn Thr Tyr Asp His
 485 490 495
 Ser Lys Tyr Arg Glu Glu Ala Met Gln Asn Arg Ile Gln Ile Asp Pro
 500 505 510
 Val Lys Leu Ser Ser Gly Tyr Lys Asp Val Ile Leu Trp Phe Ser Phe
 515 520 525
 Gly Ala Ser Cys Phe Leu Leu Leu Ala Ile Ala Met Gly Leu Val Phe
 530 535 540
 Ile Cys Val Lys Asn Gly Asn Met Arg Cys Thr Ile Cys Ile
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<210> SEQ ID NO 11

<211> LENGTH: 6907

<212> TYPE: DNA

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<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Plasmid encoding the fusion protein of SEQ ID
NO: 2

<400> SEQUENCE: 11

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 aacttacggg aaatggcccg cctggctgac cgcccaacga cccccgcca ttgacgtcaa 240
 taatgacgta tgttcccata gtaacgcca tagggacttt ccattgacgt caatgggtgg 300
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 cccctattga cgtcaatgac ggtaaattgg ccgcctggca ttatgccag tacatgacct 420
 tatgggactt tcctacttgg cagtacatct acgtattagt catcgctatt accatgggtga 480
 tgcggttttg gcagtacatc aatgggctg gatagcgggt tgactcacgg ggatttcaa 540
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 caaatgtcg taacaactcc gcccattga cgcaaatgg cggtaggcgt gtacgggtgg 660
 aggtctatat aagcagagct cgtttagtga accgtcagat cgctggaga cgccatccac 720
 gctgttttga cctccataga agacaccggg accgatccag cctccggtcg accgatcctg 780
 agaacttcag ggtgagtttg gggacccttg attgttcttt cttttctgct attgtaaaat 840
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 tgtatcacca tggaccctca tgataatttt gtttctttca ctttctactc tgttgacaac 960
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<210> SEQ ID NO 12
<211> LENGTH: 7269
<212> TYPE: DNA
<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: Plasmid encoding the fusion protein of SEQ ID
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<400> SEQUENCE: 12
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<210> SEQ ID NO 13

<211> LENGTH: 511

<212> TYPE: PRT

<213> ORGANISM: Vesicular stomatitis virus

<400> SEQUENCE: 13

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Val Pro Ser Asn Tyr His Tyr Cys Pro Ser Ser Ser Asp Leu Asn Trp
35           40           45
His Asn Asp Leu Ile Gly Thr Ala Leu Gln Val Lys Met Pro Lys Ser
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His Lys Ala Ile Gln Ala Asp Gly Trp Met Cys His Ala Ser Lys Trp
65           70           75           80
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Asp Ser Gln Phe Ile Asn Gly Lys Cys Ser Asn Tyr Ile Cys Pro Thr
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Val His Asn Ser Thr Thr Trp His Ser Asp Tyr Lys Val Lys Gly Leu
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Asp Lys Asp Leu Phe Ala Ala Ala Arg Phe Pro Glu Cys Pro Glu Gly
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Ser Ser Ile Ser Ala Pro Ser Gln Thr Ser Val Asp Val Ser Leu Ile
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Gln Asp Val Glu Arg Ile Leu Asp Tyr Ser Leu Cys Gln Glu Thr Trp
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Ser Lys Ile Arg Ala Gly Leu Pro Ile Ser Pro Val Asp Leu Ser Tyr

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Tyr Met Ile Gly His Gly Met Leu Asp Ser Asp Leu His Leu Ser Ser	405	410	415
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Val Leu Arg Val Gly Ile His Leu Cys Ile Lys Leu Lys His Thr Lys	485	490	495
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<210> SEQ ID NO 14

<211> LENGTH: 6508

<212> TYPE: DNA

<213> ORGANISM: Artificial sequence

<220> FEATURE:

<223> OTHER INFORMATION: Plasmid encoding VSV-G

<400> SEQUENCE: 14

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The invention claimed is:

1. A vector particle for transferring biological material into cells, wherein said vector particle comprises:

- a first protein which comprises the transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein, and
- a second protein which comprises a ligand of the c-Kit receptor;

wherein the first protein is represented by SEQ ID NO: 2.

2. A vector particle for transferring biological material into cells, wherein said vector particle comprises:

- a first protein which comprises the transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein, and
- a second protein which comprises a ligand of the c-Kit receptor;

wherein the second protein is represented by SEQ ID NO: 4.

3. The vector particle according to claim 1, wherein the ligand of the c-Kit receptor is the Stem Cell Factor (SCF) cytokine.

4. The vector particle according to claim 1, wherein the vector particle does not comprise the Vesicular Stomatitis Virus (VSV) G envelope glycoprotein.

5. The vector particle according to claim 1, wherein the vector particle is a lentiviral vector particle.

6. The vector particle according to claim 5, wherein the lentiviral vector particle is selected from the group consisting of HIV and SIV.

7. The vector particle according to claim 1, wherein the vector particle is intended for transferring biological material into CD34⁺ cells.

8. The vector particle according to claim 1, wherein the biological material is one or more nucleic acids.

9. The vector particle according to claim 2, wherein the first protein comprises a fusion of the transmembrane and extracellular domains of the feline endogenous RD114 virus envelope glycoprotein and the cytoplasmic domain of a retroviral envelope glycoprotein.

10. The vector particle according to claim 9, wherein the cytoplasmic domain of a retroviral envelope glycoprotein is that of Murine Leukemia Virus-A.

11. The vector particle according to claim 1, wherein the second protein comprises a fusion of a SCF cytokine and (i) the N-terminal domain of an hemagglutinin glycoprotein, or (ii) a retroviral envelope glycoprotein.

12. The vector particle according to claim 1, wherein the second protein comprises a fusion of a SCF cytokine and the N-terminal domain of an influenza virus hemagglutinin glycoprotein.

13. The vector particle according to claim 1, wherein the first and the second proteins are fused.

14. The vector particle according to claim 13, wherein the second protein comprises a SCF cytokine, optionally fused to an endoplasmic reticulum translocation signal peptide.

15. A medicament comprising a vector particle as defined in claim 1 as active ingredient.

16. An isolated protein represented by SEQ ID NO: 4.

17. An isolated nucleic acid encoding a protein according to claim 16.

* * * * *